CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-745

Name: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg

Sponsor: Impax Laboratories, Inc.

Approval Date: November 9, 2006
Full Approval – 15 mg
Tentative Approval – 5 mg and 10 mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	**X**
Labeling	**X**
Labeling Reviews	**X**
Medical Reviews	
Chemistry Reviews	**X**
Bioequivalence Reviews	**X**
Statistical Reviews	
Microbiology Reviews	
Other Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

APPROVAL LETTER

ANDA 76-745

NOV 9 2006

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
Vice President, Regulatory Affairs
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 22, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg.

Reference is also made to the tentative approval letter issued by this office on February 1, 2005, and to your amendments dated May 19, and September 17, 2004; August 29, August 31, and October 12, 2005; and January 12, and January 23, 2006. We also acknowledge receipt of your correspondences of dated July 19, August 12, and September 14, 2005, and August 31, 2006, addressing the patent issues noted below.

We have completed the review of this ANDA as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA insofar as it pertains to your Oxybutynin Chloride Extended-release Tablets 15 mg is approved, effective on the date of this letter. Because of a 180-day generic drug exclusivity issue explained below, we are unable to approve your Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg at this time. These strengths will remain **tentatively approved** and will not be eligible for final approval until the 180-day generic drug exclusivity issue noted below has been satisfactorily resolved.

The reference listed drug (RLD) upon which you have based your ANDA, Ditropan XL, Extended-release Tablets, 5 mg, 10 mg, and 15 mg, of ALZA Corporation, is subject to periods of patent protection. The following patents and expiration dates (with

pediatric exclusivity added) 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

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each listed patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 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 action was brought against IMPAX Laboratories, Inc. (IMPAX) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. This action must have been brought against IMPAX 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 notified the agency that IMPAX complied with the requirements of section 505(j)(2)(B) of the Act and that litigation for infringement of the '355 patent was brought against IMPAX within the statutory 45-day period in the United States District Court for the Northern District of California [ALZA Corporation v. IMPAX Laboratories, Inc., Civil Action No. C03-04032]. We note that IMPAX was not sued within the 45-day period on any of the other listed patents. You have also notified the agency that the district court entered a summary judgment of non-infringement in favor of IMPAX on October 6, 2005. 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 IMPAX's product does not infringe the asserted claims of the patent and that the asserted claims are invalid.

I. Approval of Oxybutynin Chloride Extended-release Tablets 15 mg

The Division of Bioequivalence has determined your Oxybutynin Chloride Extended-release Tablets, 15 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ditropan XL Extended-release Tablets, 15 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:

The dissolution testing should be conducted in:

900 mL of 0.1N HCl at 37°C using USP XXVII apparatus II (paddle) at 50 rpm for the first 2 hours; then the sample should be switched to 900 mL of phosphate buffer (with 0.2% SLS), pH 6.0, using USP apparatus II (paddle) @ 50 rpm. The test product should meet the following "interim" specifications:

2 hours	NMT (b) (4)% dissolved
4 hours	(b) (4)%
6 hours	%
14 hours	NLT (b) (4)% dissolved

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" when there are no revisions 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.

With respect to 180-day generic drug exclusivity, IMPAX was the first ANDA applicant to submit a substantially complete ANDA for Oxybutynin Chloride Extended-release Tablets, 15 mg, containing paragraph IV certifications to each patent currently listed in the "Orange Book". Therefore, with this approval, IMPAX is eligible for 180-days of market exclusivity for the Oxybutynin Chloride Extended-release Tablets, 15 mg. This exclusivity,

which is provided for under section 505(j)(5)(B)(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.

Postmarketing 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 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 all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

---

[1] Because your ANDA was filed before 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).

II. Tentative Approval of Oxybutynin Chloride Extended-release Tablets 5 mg and 10 mg

We are unable at this time to grant final approval to your ANDA at this time insofar as the 5 mg and 10 mg products because a different applicant's ANDA for Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg, containing paragraph IV certifications was received by this office prior to the receipt of your ANDA. Accordingly, as provided for in section 505(j)(5)(B)(iv) of the Act, the agency will issue a final approval of your ANDA no earlier than 180 days after the date the Secretary receives notice from the other applicant that either of the commercial marketing or court decision events provided for in section 505(j)(5)(B)(iv) has occurred.

Our decision to continue the tentative approval status of your Oxybutynin Chloride Extended-release Tablets 5 mg and 10 mg is based upon information currently available to the agency, i.e., data in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product. This decision is subject to change on the basis of new information that may come to our attention.

To reactivate your ANDA with respect to the 5 mg and 10 mg strengths prior to final approval, please submit a "MINOR SUPPLEMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that these products will be eligible for final approval. Your supplement must provide a summary of the legal basis upon which you believe the ANDA should be approved, as well as:

1. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this ANDA, or
2. a statement that no such changes have been made to the ANDA since the date of tentative approval.

Any changes in the conditions outlined in this ANDA and the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to Agency review before final approval of your Oxybutynin Chloride Extended-release Tablets 5 mg and 10 mg 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.

In addition to the supplement requested above, the agency may request at any time prior to the final date of approval that you submit an additional supplement containing the requested information. Failure to submit either supplement may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

Your Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg, may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of a drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, the 5 mg and 10 mg products will not be listed in the "Orange Book."

For further information on the status of this ANDA, or prior to submitting additional supplements, please contact Simon Eng, PharmD, Project Manager, at 301-827-5848.

Sincerely yours,

Robert Lumpkin for
11/9/2006

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

cc: ANDA 76-745
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

Robert West 8/30/06
FPL Acceptability check pending

Endorsements:
HFD-620/Y.Amin/ 12/19/05
HFD-623/A.Mueller/ 12-19-05
HFD-617/S.Eng/ 12/19/05
HFD-613/D.Catterson/ → see email fm P. Birch & John Grace
HFD-613/J.Grace/

V:\FIRMSAM\IMPAX\LTRS&REV\76745.AP.TA.~~DOC~~ → DAVE.DOC
F/T by SE

PS 1/27/06

APPROVAL/TENTATIVE APPROVAL

Approved Electronic Labeling Located at:

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\446-01 Oxybutynin 5x100S.pdf)
500 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\447-01 Oxybutynin 5x500C.pdf)
1000 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\448-01 Oxybutynin 5x1000A.pdf)
10mg
100 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\449-01 Oxybutynin 10x100S.pdf)
500 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\450-01 Oxybutynin 10x500C.pdf)
1000 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\451-01 Oxybutynin 10x1000A.pdf)
15mg
100 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\452-01 Oxybutynin 15x100S.pdf)
500 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\453-01 Oxybutynin 15x500C.pdf)
1000 tablets
Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\454-01 Oxybutynin 15x1000A.pdf)
Professional Package Insert Labeling:
Satisfactory in FPL as of January 19, 2005 submission.
(Vol. 6.1 and \\Cdsesubogd1\n76745\N_000\2005-01-19\Oxybutynin CI ER 445-02.pdf

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

TENTATIVE APPROVAL LETTER

ANDA 76-745

FEB 1 2005

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
V.P. Regulatory Affairs and Compliance
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 22, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg.

Reference is also made to your amendments dated December 29, 2003; November 12, December 6, December 8, and December 16, 2004; and January 19, 2005. We also acknowledge receipt of your correspondence dated August 18, September 8, and September 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, 5 mg, 10 mg, and 15 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, or sale of Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 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 IMPAX Laboratories, Inc. (Impax) 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 Impax 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 Impax complied with the requirements of section 505(j)(2)(B) of the Act. As a result, litigation was brought against Impax in the United States District Court for the Northern District of California involving your challenge to the '355 patent (Alza Corporation v. Impax Laboratories, Inc., Civil Action No. C-03-04032). We note that Impax 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 '355 patent is 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, the agency may request that you submit an additional amendment containing the requested information any time prior to the date of final approval of this ANDA. 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.

---

[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 Simon Eng, Project Manager, at 301-827-5848.

Sincerely yours,

Gary Buehler 2/1/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-745
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

Endorsements:
HFD-620/Y.Amin/ 1/28/05
HFD-623/A.Mueller/
HFD-617/S.Eng/ 9/14
HFD-613/D.Catterson/ for D Catterson 01/28/2005
HFD-613/J.Grace/

Bob will sign for John Grace

V:\FIRMSAM\IMPAX\LTRS&REV\76745.ta.DOC John has signed the Ap Summary on 1/27/05

F/T by

TENTATIVE APPROVAL

TA
Received
1/31/05

2/1/2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

LABELING

OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 5 MG, 10 MG AND 15 MG

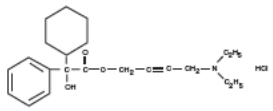
Rx only

DESCRIPTION

Oxybutynin chloride is an antispasmodic, anticholinergic agent. Each oxybutynin chloride extended release tablet contains 5 mg, 10 mg or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S- enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexyl-glycolate hydrochloride. The molecular formula of oxybutynin chloride is $C_{22}H_{31}NO_3$•HCl.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Oxybutynin chloride extended release tablets also contain the following inactive ingredients: hydrogenated vegetable oil, hypromellose type 2208/ 100,000cP, isopropyl alcohol, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, talc and triethyl citrate.

System Components and Performance

Oxybutynin chloride extended release tablets employ an enteric-coated hydrophilic hydrogel matrix to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system comprises a core, which consists of the drug, rate-controlling hydrogel and other excipients. The core is surrounded by a pH-dependent membrane. In an acidic environment such as the stomach, minimal drug release will occur due to the resistance of the pH-dependent outer membrane. Upon reaching an environment of pH 5.5 and above, the outer membrane dissolves exposing the inner core tablet, which partially hydrates to form a gel layer. Drug release is via slow diffusion out of the gel layer and subsequent gel erosion.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anticicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Following the first dose of oxybutynin chloride extended release tablets, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from oxybutynin chloride extended release tablets are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of Oxybutynin Chloride Extended Release Tablets 10 mg (n=43)

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
C_{max} (ng/mL)	1.0	(0.6)	1.8	(1.0)
T_{max} (h)	12.7	(5.4)	11.8	(5.3)
$T_{1/2}$ (h)	13.2	(6.2)	12.4	(6.1)
$AUC_{(0\ 48)}$ (ng-h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng-h/mL)	21.3	(12.2)	39.5	(21.2)

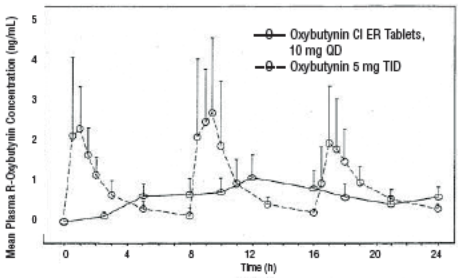


Figure 1. *Mean R-oxybutynin plasma concentrations following a single dose of oxybutynin chloride extended release tablets, 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment)*

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated oxybutynin chloride extended release tablet dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

Pharmacokinetic information for pediatric patients 5 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following oxybutynin chloride extended release tablet administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of oxybutynin chloride extended-release tablets are dose proportional.

Special Populations

Geriatric: The pharmacokinetics of oxybutynin chloride extended release tablets were similar in all patients studied (up to 78 years of age).

Pediatric: Pharmacokinetic information for pediatric patients 5 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of oxybutynin chloride extended release tablets.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of oxybutynin chloride extended release tablets.

Renal Insufficiency: There is no experience with the use of oxybutynin chloride extended release tablets in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of oxybutynin chloride extended release tablets in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS:** Drug Interactions.

Clinical Studies

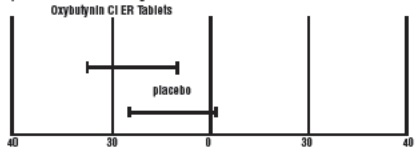
Oxybutynin chloride extended release tablets were evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following tables and figures.

Number of Urge Urinary Incontinence Episodes Per Week

Study 1	N	Oxybutynin Cl ER Tablets	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline †	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (Oxybutynin Chloride ER Tablet- Placebo)		(-13.6,-2.8)*		

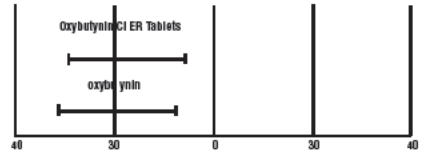
*The difference between Oxybutynin Chloride ER Tablets and placebo was statistically significant.
† Covariate adjusted mean with missing observations set to baseline values



Mean Change (+/-SD) in Episodes Per Week From Baseline

Study 2	N	Oxybutynin Cl ER Tablets	N	Oxybutynin
Mean Baseline	53	27.6	52	20.9
Mean (SD) Change from Baseline †	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (Oxybutynin Chloride ER Tablet- Oxybutynin)		(-2.8, 6.5)		

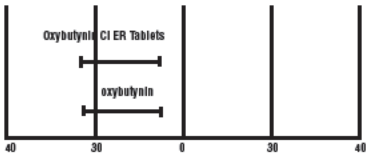
† Covariate adjusted mean with missing observations set to baseline values



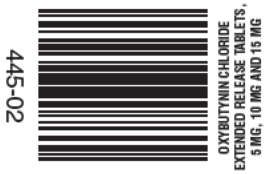
Mean Change (+/-SD) in Episodes Per Week From Baseline

Study 3	N	Oxybutynin Cl ER Tablets	N	Oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline †	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (Oxybutynin Chloride ER Tablet- Oxybutynin)		(-3.0, 1.6)**		

** The difference between oxybutynin chloride ER tablets and oxybutynin fulfilled the criteria for comparable efficacy.
† Covariate adjusted mean with missing observations set to baseline values



Mean Change (+/-SD) in Episodes Per Week From Baseline



INDICATIONS AND USAGE
Oxybutynin chloride extended release tablets are once-daily controlled-release tablets indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Pediatric use information for the treatment of patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

CONTRAINDICATIONS
Oxybutynin chloride extended release tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride extended release tablets are also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS
General
Oxybutynin chloride extended release tablets should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention:
Oxybutynin chloride extended release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders:
Oxybutynin chloride extended release tablets should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Oxybutynin chloride extended release tablets, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

Oxybutynin chloride extended release tablets should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering oxybutynin chloride extended release tablets to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients
Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that oxybutynin chloride extended release tablets should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets.

Oxybutynin chloride extended release tablets should be taken at approximately the same time each day.

Drug Interactions
The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when oxybutynin chloride extended release tablets were administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g. itraconazole and miconazole) or macrolide antibiotics (e.g. erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Concurrent ingestion of antacid (20 mL of antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone) did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed on increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects
Pregnancy Category B
Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride extended release tablet administration to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride extended release tablets should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers
It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride extended release tablets are administered to a nursing woman.

Pediatric Use
Clinical study information for pediatric patients 6 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Oxybutynin chloride extended release tablets are not recommended in pediatric patients who cannot swallow the tablet whole without chewing, dividing or crushing, or in children under the age of 6 years.

Geriatric Use
The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Special Populations:*** *Gender*).

ADVERSE REACTIONS
Adverse Events with Oxybutynin Chloride Extended Release Tablets
The safety and efficacy of oxybutynin chloride extended release tablets were evaluated in a total of 580 participants who received oxybutynin chloride extended release tablets in 4 clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Three of these studies allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from these three controlled clinical studies and one open label study in the first column in Table 2 below. Adverse events from two additional fixed dose, active controlled, 12 week treatment duration, postmarketing studies, in which 576 patients were treated with oxybutynin chloride extended release tablets 10 mg/day, are also listed in Table 2 (second column). The adverse events are reported regardless of causality.

Table 2
Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using Oxybutynin Chloride Extended-Release Tablets (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies

Body System	Adverse Event	Oxybutynin Chloride Extended-Release Tablets 5-30 mg/day (n=429)	Oxybutynin Chloride Extended-Release Tablets 10 mg/day (n=576)
General	headache	10	6
	asthenia	7	3
	pain	7	4
Digestive	dry mouth	61	29
	constipation	13	7
	diarrhea	9	7
	nausea	9	2
	dyspepsia	7	5
Nervous	somnolence	12	2
	dizziness	6	4
Respiratory	rhinitis	6	2
Special senses	blurred vision	8	1
	dry eyes	6	3
Urogenital	urinary tract infection	5	5

The most common adverse events reported by patients receiving 5-30 mg/day of oxybutynin chloride extended release tablets were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to <5% of the 429 patients who received 5-30 mg/day of oxybutynin chloride extended release tablets in the 4 efficacy and safety studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilatation; *Digestive:* flatulence, gastroesophageal reflux; *Musculoskeletal:* arthritis; *Nervous:* insomnia, nervousness, confusion; *Respiratory:* upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin:* dry skin, rash; *Urogenital:* impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with oxybutynin chloride extended release tablets include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSAGE
The continuous release of oxybutynin from oxybutynin chloride extended release tablets should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION
Oxybutynin chloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

Oxybutynin chloride extended-release tablets may be administered with or without food.

Adults: The recommended starting dose of oxybutynin chloride extended release tablets is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general dosage adjustment may proceed at approximately weekly intervals.

Pediatric patients: Dosing information for pediatric patients aged 6 years and older is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

HOW SUPPLIED
Oxybutynin chloride extended-release tablets, 5 mg—Each purple, film-coated, round convex tablets, debossed with "G 341" on one side and plain on the other side
Bottles of 100 NDC 0115-3411-01
Bottles of 500 NDC 0115-3411-02
Bottles of 1000 NDC 0115-3411-03

Oxybutynin chloride extended-release tablets, 10 mg—Each pink, film-coated, round convex tablets, debossed with "G 342" on one side and plain on the other side
Bottles of 100 NDC 0115-3422-01
Bottles of 500 NDC 0115-3422-02
Bottles of 1000 NDC 0115-3422-03

Oxybutynin chloride extended-release tablets, 15 mg—Each off-white, film-coated, round convex tablets, debossed with "G 343" on one side and plain on the other side
Bottles of 100 NDC 0115-3433-01
Bottles of 500 NDC 0115-3433-02
Bottles of 1000 NDC 0115-3433-03

Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]. Protect from moisture and humidity.

Dispense in a tightly-closed, light-resistant container (USP).

Mfg. by:
IMPAX Laboratories, Inc.
Hayward, CA 94544

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rx only

Rev. 01/2005
445-02

(b) (4)

proof date	10/21/04	10/28/04	11/2/04	
proof #	1	2	3	
proof date				
proof #				

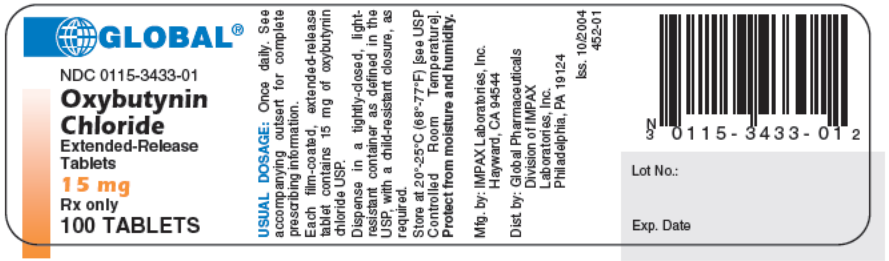
proof approval form

(b) (4)

NOTE: Proof colors do not represent exact PMS colors. Please check current PMS guide.

- Black
- Blue PMS (b) (4)
- Orange PMS (b) (4)

Wind direction #4



unvarnished area

Customer: Global: Oxybubynin Chloride 15 mg 100 tablets (ER)

P.O. No #:

Job number: GP314

Size: S 1-1/4" x 4-1/2"

Comments: 452-01

PROOFREAD INTERNALLY BY:	DATE:

Reviewed by:	Date

Submit Revised Proof:	Date
Proof Approved By:	Date

CG007-01

(b) (4)

proof date	10/21/04	10/28/04	11/2/04	
proof #	1	2	3	
proof date				
proof #				

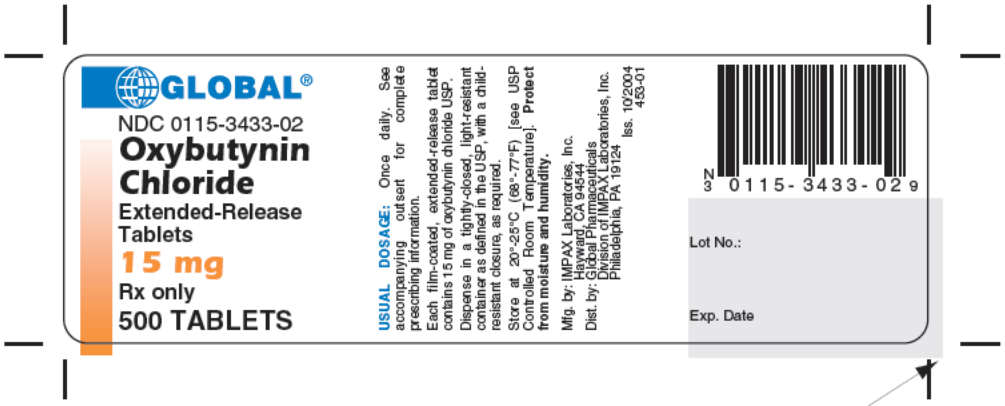
proof approval form

(b) (4)

NOTE: Proof colors do not represent exact PMS colors. Please check current PMS guide.

- Black
- Blue PMS (b) (4)
- Orange PMS (b) (4)

Wind direction #4



unvarnished area

Customer: Global: Oxybubynin Chloride 15 mg 500 tablets (ER)

P.O. No #:

Job number: GP316

Size: C 1-1/2" x 4-1/2"

Comments: 453-01

PROOFREAD INTERNALLY BY:	DATE:

Reviewed by:	Date

Submit Revised Proof:	Date
Proof Approved By:	Date

CG007-01

(b) (4)

proof date	10/21/04	10/28/04	11/2/04	11/4/04
proof #	1	2	3	4
proof date	11/18/04			
proof #	5			

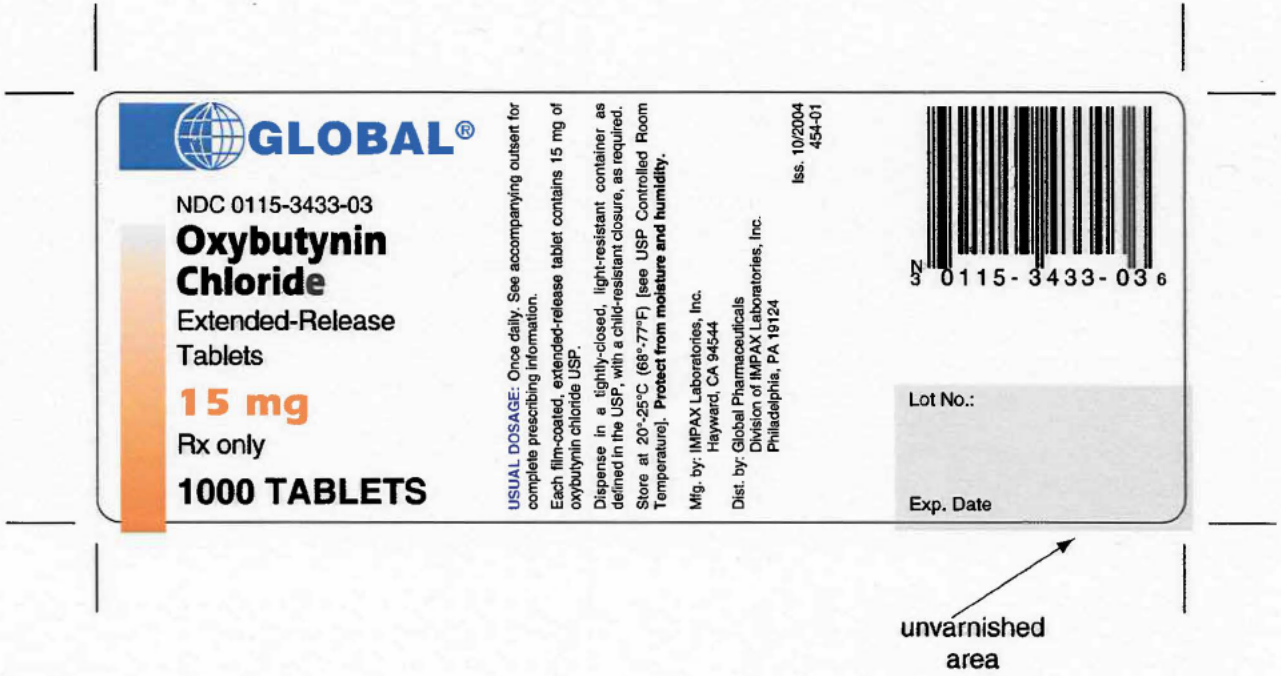
proof approval form

(b) (4)

NOTE: Proof colors do not represent exact PMS colors. Please check current PMS guide.

- **Black**
- **Blue PMS** (b) (4)
- **Orange PMS** (b) (4)

Wind direction #4



Global:

Customer: **Oxybutynin Chloride 15 mg 1000 Tablets (ER)**

P.O. No #:

Job number: **GP315**

Size: **A 2-3/8" x 6"**

Comments: **454-01**

PROOFREAD INTERNALLY BY:	DATE:

Reviewed by:	Date

Submit Revised Proof:	Date
Proof Approved By:	Date

CG007-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

LABELING REVIEWS

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

ANDA Number: 76-745 Dates of Submission: May 22, 2003, August 14, 2003, December 6, 2004 and January 19, 2005

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 5mg, 10 mg and 15 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (Bottles of 100, 500 and 1000 tablets)

5mg

100 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\446-01 Oxybutynin 5x100S.pdf)

500 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\447-01 Oxybutynin 5x500C.pdf)

1000 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\448-01 Oxybutynin 5x1000A.pdf)

10mg

100 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\449-01 Oxybutynin 10x100S.pdf)

500 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\450-01 Oxybutynin 10x500C.pdf)

1000 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\451-01 Oxybutynin 10x1000A.pdf)

15mg

100 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\452-01 Oxybutynin 15x100S.pdf)

500 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\453-01 Oxybutynin 15x500C.pdf)

1000 tablets

Satisfactory in FPL as of December 6, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76745\N_000\2004-12-06\454-01 Oxybutynin 15x1000A.pdf)

Professional Package Insert Labeling:
Satisfactory in FPL as of January 19, 2005 submission.
(Vol. 6.1 and \\Cdsesubogd1\n76745\N_000\2005-01-19\Oxybutynin CI ER 445-02.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
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

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

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	

3. MANUFACTURING FACILITY

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544
(Vol. A1.2, p 003471)

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 tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.

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/CONTAINER CLOSURE:

NDA- bottles of 16 fluid ounces (473 mL)

ANDA- The 5 mg, 10 mg and 15 mg tablets will be packaged in 100 counts (50 cc), 500 counts (150cc) and1000 counts (500cc). See section XIII.3

Description of Containers:

PACKAGE SIZE FOR 5, 10 AND 15 MG TABLETS	BOTTLE	CLOSURE
100's count	50 cc HDPE white bottles	33/400 fine-ribbed plastic white cap,

PACKAGE SIZE FOR 5, 10 AND 15 MG TABLETS	BOTTLE	CLOSURE
		with (b) (4) printed liner
500's count	150cc HDPE white bottles	38/400 fine-ribbed plastic white cap, with (b) (4) printed liner
1000's count	500cc HDPE white bottles	53/400 fine-ribbed plastic white cap, with (b) (4) printed liner

(Vol. A1.2, p. 003702)

Date of Review: January 28, 2005

Dates of Submission: May 22, 2003, August 14, 2003, December 6, 2004 and January 19, 2005

Primary Reviewer: Postelle Birch Date: January 28, 2005 1/28/05

Team Leader: John Grace Date: 1/27/05

---

cc: ANDA: 76-745
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\76-745ap.label.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

CHEMISTRY REVIEWS

ANDA #76-745

Oxybutynin Chloride Extended-Release Tablets 5 mg, 10 mg, and 15 mg

Impax Laboratories Inc.

Yusuf Amin

Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-745

2. REVIEW #: 1

3. REVIEW DATE: 01-OCT-2003

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Original	22-MAY-2003
Amendment	14-AUG-2003

7. NAME & ADDRESS of APPLICANT:

Name:	Impax Laboratories Inc.
Address:	30831 Huntwood Avenue Hayward, CA 94544
Representative:	Mr. Mark C. Shaw
Telephone:	510-476-2018
Fax:	510-476-2091

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)(iv)
Based on RLD: Alza's Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)
There are ten patents, eight with associated pediatric exclusivities, that relate to the RLD.
The firm has provided Paragraph II, III and IV Patent Certifications - see pages 000008 to 000010. The firm has also provided a statement about the exclusivity for New Patient Population and Pediatric extension (both expire on 4/15/2006) in the Amendment Section III.

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: Tablets

12. STRENGTH / POTENCY: 5 mg, 10 mg and 15 mg

13. ROUTE of ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

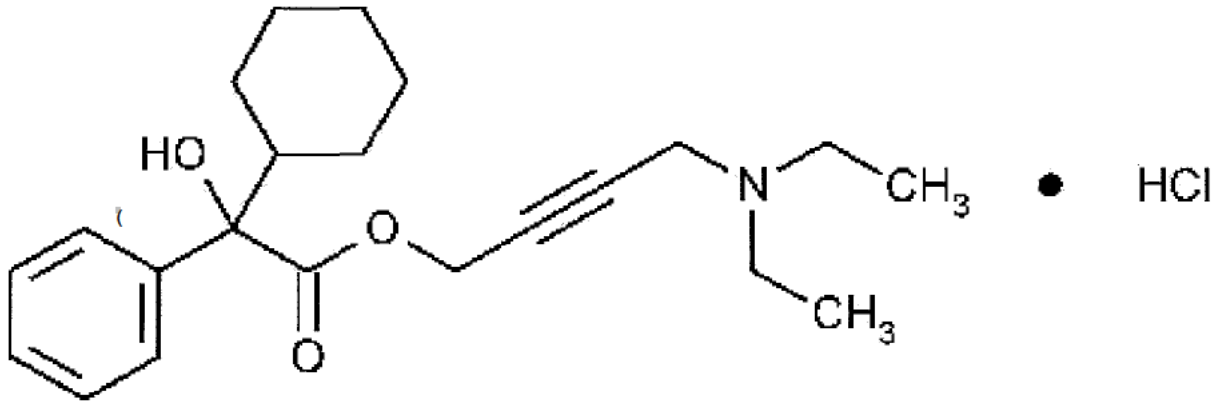
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

$C_{22}H_{31}NO_3 \cdot HCl$ 393.95
Benzeneacetic acid, a-cyclohexyl-a-hydroxy-, 4-(diethylamino)-2-butynyl ester hydrochloride, (±)-.
4-(Diethylamino)-2-butynyl (±)-a-phenylcyclohexaneglycolate hydrochloride [1508-65-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's**:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	31-OCT-2003	Reviewed by S. Pope
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[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
NDA for Ditropan XL	20-897	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	15-SEP-2003	J.D Ambrogio
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
Env. Assessment	N/A		
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 If no, explain reason below:

The Chemistry Review for ANDA 76-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval at this time bio and other issues.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin Chloride drug substance is referenced as a USP monograph. Chemical name: 4-(Diethylamino)-2-butylnyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.95. It is a white to off-white powder melting between 124°C to 129°C. Extensive review of the literature and testing by (b) (4) the manufacturer of the API, showed no evidence of polymorphism. This API is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane.

The firm has conducted two bio-equivalency studies. In these studies, a single dose of Oxybutynin Chloride extended release tablets 15 mg manufactured by Impax Laboratories, Inc. was compared with Ditropan XL 15 mg Tablets distributed by Alza Pharmaceuticals. These studies were a single dose fasting study and a single dose limited food effects study. The data are provided to compare the relative bioavailability (rate and extent of absorption) of two products. The firm has filed waivers for in-vivo bio-equivalency for the 5 mg and 10 mg strengths.

The manufacturing and testing of the drug product is performed at the Hayward, California facility, however packaging and labeling is done at Global Pharmaceuticals (division of Impax Laboratories) in Philadelphia, PA. The manufacturing of Oxybutynin Chloride extended release tablets involves a (b) (4) (b) (4).

The brief synopsis of the tablets manufacture is as follows. (b) (4)

The drug product is not USP compendial. The company has develop and validated an analytical method for the drug product.

The Referenced Listed Drug, i.e. Alza's Ditropan XL Tablets, use Alza's Push-Pull™ patented delivery system. This controlled release system is based on osmosis for delivery of the active drug, wherein the "tablet" consist of a "push" layer and a drug layer contained in a (b) (4) based membrane. This membrane has a laser – drilled hole for release of the drug. This application uses conventional enteric tablet coating for the extended release properties of this drug product. The difference in delivery of these drug products should be evaluated by the Division of Bio-equivalence.

This ANDA is found to be deficient and the deficiencies are highlighted in bold letters in the text. The deficiencies noted will be communicated to the applicant.

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 XL Tablets.

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted.

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsement Block

Chemist Name/Date:	Yusuf Amin./11/10/03
ChemistryTeamLeaderName/Date:	Al Mueller Ph.D./11/10/03
Project Manager Name & Date:	Craig Kiester, PM/11/10/03

11/12/03
11-12-03
11/12/03

C. CC Block

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV1.doc

Following this page, 16 pages withheld in full - (b)(4)

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

The drug product is not an USP compendial item. However, the method validation for Drug substance and residual solvents are deficient. After the these issues are resolved it will be determined if method validation by the FDA Laboratory is necessary.

32. LABELING: Pending

33. ESTABLISHMENT INSPECTION: Satisfactory

The Overall recommendation: Acceptable 15-SEP-2003 (J.D Ambrogio HFD-322).

34. BIOEQUIVALENCE: Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION: Satisfactory

The applicant claims a categorical exclusion under an environmental assessment under 21 CFR 25.31. (See page 004015 Volume 1.14)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-745 APPLICANT: Impax Laboratories Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. We note your proposed specification for [redacted] (b) (4) as shown on their Certificate of Analysis.

2. We recommend the inclusion of a [redacted] (b) (4) test/specification for release and stability of these drug products.

3. The limits for [redacted] (b) (4) should be revised to correspond to the [redacted] (b) (4) We recommend that you [redacted] (b) (4) acceptance criteria for release testing for all strengths to agree more closely with your reported data.

4. We suggest that the [redacted] (b) (4)

5. [redacted] (b) (4)

6. The limits for [redacted] (b) (4) acceptance criteria for stability for all strengths to agree more closely with your reported data.

7. [redacted] (b) (4) does not meet the specification (Page 003623, Volume 1.13). Please explain.

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

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. Your labeling information is currently under review. Any deficiencies will be communicated to you under separate cover.

3. Please provide updated room temperature stability data from the ANDA exhibit batches.

4. We have noted that you intend to (b) (4) in consultation with the local district of the agency.

5. The firms referenced in your ANDA application relative to the manufacturing, packaging and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 76-745
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Yusuf A. Amin /11/10/2003 11/12/03

HFD-623/ Albert J. Mueller Ph.D. /11/10/03 11-12-03

HFD-617/ C.Kiester /PM /11/10/03 11/12/03

F/T by:ard/11/10/03

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV1.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

ANDA #76-745

Oxybutynin Chloride Extended-release Tablets 5 mg, 10 mg, and 15 mg

IMPAX Laboratories, Inc.

Yusuf Amin

Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-745
2. REVIEW #: 3 ~~#~~ 2
3. REVIEW DATE: 10-DEC-2004
4. REVIEWER: Yusuf Amin
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original	22-MAY-2003
Amendment	14-AUG-2003
Amendment	29-DEC-2003

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	12-NOV-2004
Amendment	15-NOV-2004
Amendment	08-DEC-2004
Amendment	16-DEC-2004
Amendment (Labeling)	19-JAN-2005

7. NAME & ADDRESS of APPLICANT:

Name:	Impax Laboratories Inc.
Address:	30831 Huntwood Avenue Hayward, CA 94544
Representative:	Mr. Mark C. Shaw
Telephone:	510-476-2018
Fax:	510-476-2091

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS For SUBMISSION:
505(j)(2)(A)(vii)(iv)
Based on RLD: Alza's Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)
There are ten patents, eight with associated pediatric exclusivities, that relate to the RLD.
The firm has provided Paragraph II, III and IV Patent Certifications - see pages 000008 to 000010. The firm has also provided a statement about the exclusivity for New Patient Population and Pediatric extension (both expire on 4/15/2006) in the Amendment Section III.

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: Tablets

12. STRENGTH / POTENCY: 5 mg, 10 mg and 15 mg

13. ROUTE of ADMINISTRATION: Oral

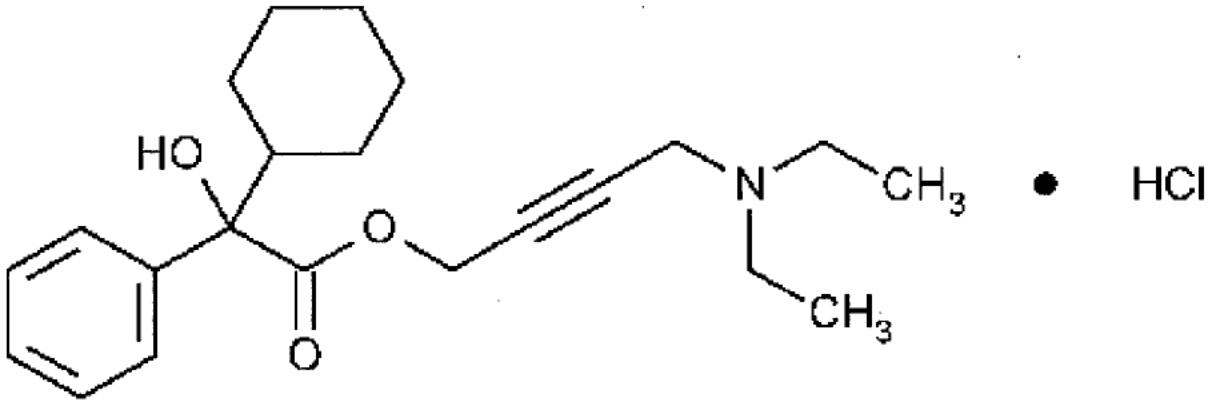
14. R*x*/OTC DISPENSED: R*x*

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:
$C_{22}H_{31}NO_3 \cdot HCl$ 393.95
Benzeneacetic acid, a-cyclohexyl-a-hydroxy-, 4-(diethylamino)-2-butynyl ester hydrochloride, (±)-.
4-(Diethylamino)-2-butynyl (±)-a-phenylcyclohexaneglycolate hydrochloride [1508-65-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	04-DEC-2004	Reviewed by M. Darj
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[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
NDA for Ditropan XL	20-897	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	15-SEP-2003	J.D Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	27-JAN-2005	P. Birch
Bioequivalence	Acceptable	22-OCT-2004	J. Lee
Env. Assessment	N/A		
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 If no, explain reason below:

The Chemistry Review for ANDA 76-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC is approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin Chloride drug substance is referenced as a USP monograph. Chemical name: 4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.95. It is a white to off-white powder melting between 124°C to 129°C. Extensive review of the literature and testing by (b) (4) the manufacturer of the API, showed no evidence of polymorphism. This API is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane.

The firm has conducted two bio-equivalency studies. In these studies, a single dose of Oxybutynin Chloride extended release tablets 15 mg manufactured by Impax Laboratories, Inc. was compared with Ditropan XL 15 mg Tablets distributed by Alza Pharmaceuticals. These studies were a single dose fasting study and a single dose limited food effects study. The data are provided to compare the relative bioavailability (rate and extent of absorption) of two products. The firm has filed waivers for in-vivo bio-equivalency for the 5 mg and 10 mg strengths.

The manufacturing and testing of the drug product is performed at the Hayward, California facility, however packaging and labeling is done at Global Pharmaceuticals (division of Impax Laboratories) in Philadelphia, PA. The manufacturing of Oxybutynin Chloride extended release tablets involves a (b) (4) (b) (4)

The brief synopsis of the tablets manufacture is as follows. (b) (4)

The drug product is not USP compendial. The company has develop and validated an analytical method for the drug product.

The Referenced Listed Drug, i.e. Alza's Ditropan XL Tablets, use Alza's Push-Pull™ patented delivery system. This controlled release system is based on osmosis for delivery of the active drug, wherein the "tablet" consist of a "push" layer and a drug layer contained in a (b) (4) based membrane. This membrane has a laser – drilled hole for release of the drug. This application uses conventional enteric tablet coating for the extended release properties of this drug product.

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

Oxybutynin Chloride extended release tablets is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The name given by the innovator is Ditropan XL Tablets. The Maximum Daily Dosage is 30 mg/Day.

C. Basis for Approvability or Not-Approval Recommendation

CMC is approvable.

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsement Block

Chemist Name/Date:	Yusuf Amin./12/20/04 1/28/05
ChemistryTeamLeaderName/Date:	Al Mueller Ph.D./ 1-28-05
Project Manager Name & Date:	S. Eng, PM/

C. CC Block

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV3.doc

Following this page, 13 pages withheld in full - (b)(4)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:
Satisfactory

The applicant claims a categorical exclusion under an environmental assessment under 21 CFR 25.31. (See page 004015 Volume 1.14)

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA # 76-745
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-623/Yusuf A. Amin /12/20/2004 1/28/05
HFD-623/ Albert J. Mueller Ph.D. / 1-28-05
HFD-617/ S.Eng /PM / 1/28/05

F/T by:

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV3.doc

TYPE of LETTER: APPROVABLE

ANDA #76-745

Oxybutynin Chloride Extended-release Tablets 5 mg, 10 mg, and 15 mg

IMPAX Laboratories, Inc.

Yusuf Amin

Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-745

2. REVIEW #: 4

Appears to be a numbering error. This is thought to be Chemistry Review #3.

3. REVIEW DATE: 13-JAN-2006

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	22-MAY-2003
Amendment	14-AUG-2003
Amendment	29-DEC-2003

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	12-NOV-2004
Amendment	15-NOV-2004
Amendment	08-DEC-2004
Amendment	16-DEC-2004
Amendment (Labeling)	19-JAN-2005
Amendment (Telephone)	12-JAN-2006
Amendment (Telephone)	23-JAN-2006

7. NAME & ADDRESS of APPLICANT:

Name:	Impax Laboratories Inc.
Address:	30831 Huntwood Avenue Hayward, CA 94544
Representative:	Mr. Mark C. Shaw
Telephone:	510-476-2018
Fax:	510-476-2091

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS For SUBMISSION:
505(j)(2)(A)(vii)(iv)
Based on RLD: Alza's Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)
There are ten patents, eight with associated pediatric exclusivities, that relate to the RLD.
The firm has provided Paragraph II, III and IV Patent Certifications - see pages 000008 to 000010. The firm has also provided a statement about the exclusivity for New Patient Population and Pediatric extension (both expire on 4/15/2006) in the Amendment Section III.

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: Tablets

12. STRENGTH / POTENCY: 5 mg, 10 mg and 15 mg

13. ROUTE of ADMINISTRATION: Oral

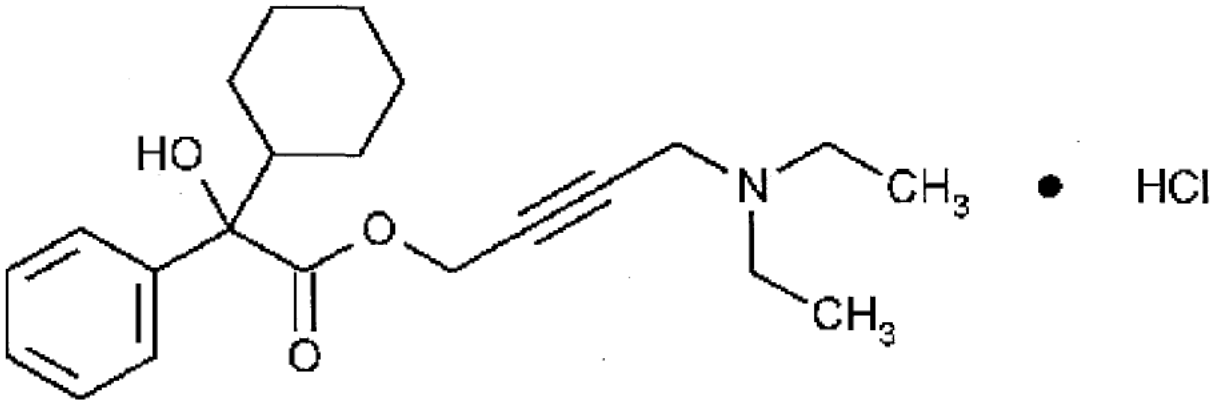
14. R*x*/OTC DISPENSED: R*x*

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:
$C_{22}H_{31}NO_3 \cdot HCl$ 393.95
Benzeneacetic acid, a-cyclohexyl-a-hydroxy-, 4-(diethylamino)-2-butynyl ester hydrochloride, (±)-.
4-(Diethylamino)-2-butynyl (±)-a-phenylcyclohexaneglycolate hydrochloride [1508-65-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	04-DEC-2004	Reviewed by M. Darj
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[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
NDA for Ditropan XL	20-897	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	15-SEP-2003	J.D Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	27-JAN-2005	P. Birch
Bioequivalence	Acceptable	22-OCT-2004	J. Lee
Env. Assessment	N/A		
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 If no, explain reason below:

The Chemistry Review for ANDA 76-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC is approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin Chloride drug substance is referenced as a USP monograph. Chemical name: 4-(Diethylamino)-2-butylnyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.95. It is a white to off-white powder melting between 124°C to 129°C. Extensive review of the literature and testing by (b) (4) the manufacturer of the API, showed no evidence of polymorphism. This API is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane.

The firm has conducted two bio-equivalency studies. In these studies, a single dose of Oxybutynin Chloride extended release tablets 15 mg manufactured by Impax Laboratories, Inc. was compared with Ditropan XL 15 mg Tablets distributed by Alza Pharmaceuticals. These studies were a single dose fasting study and a single dose limited food effects study. The data are provided to compare the relative bioavailability (rate and extent of absorption) of two products. The firm has filed waivers for in-vivo bio-equivalency for the 5 mg and 10 mg strengths.

The manufacturing and testing of the drug product is performed at the Hayward, California facility, however packaging and labeling is done at Global Pharmaceuticals (division of Impax Laboratories) in Philadelphia, PA. The manufacturing of Oxybutynin Chloride extended release tablets involves a (b) (4) (b) (4).

The brief synopsis of the tablets manufacture is as follows. (b) (4)

The drug product is not USP compendial. The company has develop and validated an analytical method for the drug product.

The Referenced Listed Drug, i.e. Alza's Ditropan XL Tablets, use Alza's Push-Pull™ patented delivery system. This controlled release system is based on osmosis for delivery of the active drug, wherein the "tablet" consist of a "push" layer and a drug layer contained in a (b) (4) based membrane. This membrane has a laser – drilled hole for release of the drug. This application uses conventional enteric tablet coating for the extended release properties of this drug product.

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

Oxybutynin Chloride extended release tablets is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The name given by the innovator is Ditropan XL Tablets. The Maximum Daily Dosage is 30 mg/Day.

C. Basis for Approvability or Not-Approval Recommendation

CMC is approvable.

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsement Block

Chemist Name/Date:	Yusuf Amin./01/25/06 1/25/06
ChemistryTeamLeaderName/Date:	Al Mueller Ph.D./ 1-25-06
Project Manager Name & Date:	S. Eng, PM/ 1/27/06

C. CC Block

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV4.doc

Following this page, 13 pages withheld in full - (b)(4)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:
Satisfactory

The applicant claims a categorical exclusion under an environmental assessment under 21 CFR 25.31. (See page 004015 Volume 1.14)

cc: ANDA # 76-745
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-623/Yusuf A. Amin /01/25/2006 1/25/06
HFD-623/ Albert J. Mueller Ph.D. / 1-25-06
HFD-617/ S.Eng /PM / 1/27/06

F/T by:

V:\FIRMSAM\IMPAX\LTRS&REV\76745.REV4.doc

TYPE of LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-745
Drug Product Name	Oxybutynin chloride ER tablet
Strength	5, 10 and 15 mg
Applicant Name	Impax Laboratories, Inc.
Address	Hayward, California
Submission Date(s)	22 May 2003
Amendment Date(s)	14 Aug 2003 (to include waiver requests for the 5 & 10 mg tablets)
Reviewer	**J. Lee**
First Generic	**yes**
File Location	**V:\firmsam\Impax\ltrs&rev\76745N803.doc**

I. Executive Summary

This application pertains to oxybutynin Cl ER 5, 10 and 15 mg tablets [vs RLD Ditropan XL®] and includes one fasting and one fed BE study on the 15 mg tablet. The fasting study is a single-dose, two-way crossover study using 48 healthy normal male and female volunteers [45 completing] given a dose of 15 mg. The results (point estimate, 90% CI) of the fasting BE study are [oxybutynin] LAUCt of 101, 90.4-112%; LAUCi of 100, 89.9-112%; and LCmax of 97.5, 85.2-112%; [desethyloxybutynin] LAUCt of 94.9, 86.1-105%; LAUCi of 95.3, 86.3-105%; and LCmax of 93.7, 82.6-106%. The fed BE study is a single-dose two-way crossover study using 30 healthy normal male and female volunteers [29 completing] given a dose of 15 mg. The results (point estimate) of the fed BE study are [oxybutynin] AUCt of 107; AUCi of 101 and Cmax of 109; [desethyloxybutynin] AUCt of 94.2; AUCi of 94.3 and Cmax of 101. Since the fed study was initiated prior to the issuance of the BA/BE Food Guidance, confidence intervals were not calculated in the fed study. Waiver requests for the 5 and 10 mg tablets were deferred due to the outstanding deficiencies. Dissolution testing data was submitted using the sponsor's in-house method and was found incomplete. This application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	oxybutynin Cl ER tablet
Reference Product	**Ditropan XL® tablet**
RLD Manufacturer	**Alza Corporation**
NDA No.	**20-897**
RLD Approval Date	**22 June 1999**
Indication	**to treat overactive bladder with symptoms of urge urinary incontinence, urgency and frequency**

B. PK/PD Information

Bioavailability	**6%**
Food Effect	none
Tmax	**4-6 hrs**
Metabolism	primarily metabolized by the cytochrome P450 enzyme systems; one metabolic product, desethyloxybutynin, is active.
Excretion	< 0.1% of oxybutynin or desethyloxybutynin appears in the urine unchanged
Half-life	16 hrs (fasting) and 12 hrs (post-prandial)
Relevant OGD or DBE History	OGD has received the following oxybutynin Cl ER tablet ANDAs: 76-644 (Mylan - 10 mg tab)
Agency Guidance	**none**
Drug Specific Issues (if any)	Control docs #00-025 and 01-297 recommend that oxybutynin and desethyloxybutynin be measured. The metabolite is formed as a result of presystemic metabolism and is active.

C. Contents of Submission

Study Types		How many?
Single-dose fasting	x	1
Single-dose fed	x	1
In vitro dissolution	x	3
Waiver requests	x	2

D. Pre-Study Bioanalytical Method Validation

Analyte name	oxybutynin	desethyloxybutynin
Internal Standard	(b) (4)	(b) (4)
Method description	LC/MS/MS	LC/MS/MS
QC range	0.200 to 20.0 ng/ml	0.500 to 100 ng/ml
Standard curve range	0.100 to 25.0 ng/ml	0.500 to 125 ng/ml
Limit of quantitation	0.100 ng/ml	0.500 ng/ml
Average recovery of Drug (%)	90.9%	88.7%
Average Recovery of Int. Std (%)	101%	101%
Intraday precision range (%CV)	2.03 to 4.09%	3.77 to 5.04%
Intraday accuracy range (%)	98.3 to 103%	97.3 to 102%
Interday precision range (%CV)	3.73 to 9.69%	1.98 to 15.1%
Interday accuracy range (%)	95.6 to 108%	92.8 to 109%
Bench-top stability (hrs)	6 hrs	72 hrs
Stock stability (days)	1 month	1 month
Processed stability (hrs)	48 hrs	48 hrs
Freeze-thaw stability (cycles)	3 cycles	3 cycles
Long-term storage stability (days)	53	53
Dilution integrity	2-fold, 98.8%	2-fold, 111%
Specificity	y	y
SOPs submitted	y	y
20% Chromatograms included (Y/N)	y	y
Random Selection of Serial Chrom	y	y

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R03-068
Study Design	single-dose, two-way crossover
No. of subjects enrolled	48
No. of subjects completing	45
No. of subjects analyzed	45
Subjects (Normal/Patients?)	normals
Sex(es) included (how many?)	Male: 29 Female: 19
Test product	oxybutynin Cl ER tablet
Reference product	Ditropan XL® tablet
Strength tested	15 mg
Dose	1 x 15 mg

Summary of Statistical Analysis (oxybutynin) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	101	90.4; 112
AUC∞	100	89.9; 112
Cmax	97.5	85.2; 112
Summary of Statistical Analysis (desethyloxybutynin) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	94.9	86.1; 105
AUC∞	95.3	86.3; 105
Cmax	93.7	82.6; 106

Reanalysis of Study Samples (oxybutynin) 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**
questionable result	**1**	**2**	**0.05**	**0.1**	**1**	**2**	**0.05**	**0.1**
Total	**1**	**2**	**0.05**	**0.1**	**1**	**2**	**0.05**	**0.1**

Reanalysis of Study Samples (desethyloxybutynin) 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								
Total								

Did use of recalculated plasma concentration data change study outcome? no

2. Single-dose Fed Bioequivalence Study

Study No.	RA2-200
Study Design	randomized, single-dose two-way crossover
No. of subjects enrolled	30
No. of subjects completing	29
No. of subjects analyzed	29
Subjects (Normal/Patients?)	normals
Sex(es) included (how many?)	Male 21 Female 9
Test product	oxybutynin Cl ER tablet
Reference product	Ditropan XL® ER tablet
Strength tested	15 mg
Dose	1 x 15 mg

Summary of Statistical Analysis (oxybutynin) Additional Information in Appendix, Table 16 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	107	N/A*
AUC∞	101	N/A*
Cmax	109	N/A*
Summary of Statistical Analysis (desethyloxybutynin) Additional Information in Appendix, Table 16 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	94.2	N/A*
AUC∞	94.3	N/A*
Cmax	101	N/A*

*Since this study was initiated prior to the issuance of the BA/BE Food Guidance, the sponsor did not calculate the confidence intervals.

Reanalysis of Study Samples (oxybutynin) Additional information in Appendix, Table 15								
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 PK repeats								
Total								

Reanalysis of Study Samples (desethyloxybutynin) Additional information in Appendix, Table 15								
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 PK repeats								
Total								

Did use of recalculated plasma concentration data change study outcome? no

F. Formulation

The test product formulation is detailed in Table 1 of the Appendix.

G. In Vitro Dissolution

USP apparatus II (paddle) @ 100 rpm
900 ml of pH 6.0 phosphate buffer w/0.2% SLS
Drug release:
1 hr (b) (4)%
2 hr %
4 hr %
8 hr NLT (b) (4)%

The above dissolution method is the sponsor's proposed method.

H. Waiver Request(s)

Strengths for which waivers requested	5 and 10 mg
Regulation cited	21 CFR 320.22 (d)(2)
Proportional to strength tested in vivo	Y
Dissolution is acceptable	N/A
Waiver granted	N/A

I. Deficiency Comments

1. The sponsor should submit long-term stability data that indicates the frozen samples are stable for the duration of the fasted study [from first administration to last sample analyzed - 74 days]. The sponsor has submitted stability data that shows long-term stability for only 53 days.

2. The sponsor should explain whether there were any sample repeat analyses for desethyloxybutynin in the fasted study. That table is missing from the study report. The sponsor should also submit the formal SOP governing Repeat Sample Analyses.

3. The sponsor should conduct additional dissolution testing as follows using the 15 mg test product bio-batch and a fresh batch of 15 mg Ditropan XL®, since the reference bio-batch has expired:

   a. 900 ml of water
   apparatus I (basket) @ 100 rpm and
   apparatus II (paddle) @ 50 rpm

   b. 900 ml of acetate buffer, pH 4.5
   apparatus I (basket) @ 100 rpm and
   apparatus II (paddle) @ 50 rpm

   c. 900 ml of 0.1N HCl
   apparatus I (basket) @ 100 rpm and
   apparatus II (paddle) @ 50 rpm

For methods a, b and c, a small amount of sodium lauryl sulfate may be added to facilitate dissolution if it can be shown to be necessary.

   d. 50 ml of simulated gastric fluid w/o enzyme
   apparatus VII (reciprocating disk)
   30 cycles/minute, 2-3 cm

The sponsor should sample at 1, 2, 4, 6, 8, 10 and 12 hrs or until at least 80% of the drug is released. The sponsor should choose the best method and then conduct comparative dissolution testing with the 5 mg and 10 mg tablets vs the corresponding strength of the RLD using the best method. All raw data should be submitted with means at each sampling point, %CVs, minimum value and maximum value tabulated.

J. Recommendations

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute and (b) (4) for Impax Laboratories, Inc. on its oxybutynin Cl ER 15 mg tablet have been found incomplete due to comments #1-3.

   The sponsor should address comments #1-3.

R. Lee 12/18/04

J. Lee, Branch II

2/19/2004

SGNerurkar, Ph.D., Team Leader, Branch II

for Barbara M Davit 2/19/04

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	R03-068
Study Title	A Relative bioavailability study of 15 mg oxybutynin chloride extended release tablets under fasting conditions.
Clinical Site	PRACS Institute, Ltd.; Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	per I - 15 Feb 03; per II - 1 Mar 03
Analytical Site	(b) (4)
Analytical Director	(b) (6), Ph.D.
Analysis Dates	11 Mar 03 - 29 Apr 03
Storage Period (no. of days from first sample to final analysis)	74 days

Treatment ID	A	B
Test or Reference	test	reference
Product Name	oxybutynin Cl ER tablet	**Ditropan XL® ER tablet**
Manufacturer	Impax Laboratories	**Alza Corporation**
Batch/Lot No.	R02043-100B	0117620
Manufacture Date	27 Nov 02	N/A
Expiration Date	N/A	Dec, 2003
Strength	15 mg	15 mg
Dosage Form	tablet	tablet
Batch Size	(b) (4) dosage units	N/A
Production Size	(b) (4) dosage units	N/A
Potency	97.7%	97.0%
Content Uniformity	97.6%	97.0%
Dose Administered	1 x 15 mg	1 x 15 mg
Route of Administration	oral	oral

No. of Sequences	**2**
No. of Periods	**2**
No. of Treatments	**2**

No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB - subj 1, 6, 7, 12, 13, 15, 22, 23, 24, 27, 31, 32, 33, 34, 36, 38, 39, 40, 41, 42, 44, 46, 47, 48 BA - subj 2, 3, 4, 5, 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, 21, 25, 26, 28, 29, 30, 35, 37, 43, 45
Blood Sampling Times	0 (pre-dose), 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 48, 60 and 72 hrs
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	centrifuge, decant plasma and store at -20°C
IRB Approval	y
Informed Consent	y
Subjects Demographics	See Table 1
Length of Fasting	overnight
Length of Confinement	1 day pre-dose until 24 hrs post-dose
Safety Monitoring	BP, pulse obtained at zero hr and at 12 and 24 hr

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	90
Mean	25.8	Mean	162	18-40	90	Male	60	Afr. Amer.	6
SD	9.1	SD	28.2	41-64	10	Female	40	Hispanic	4
Range	18-50	Range	103-236	65-75	0			Asian	
				>75				Others	

Study Results

Table 2 Dropout Information

Subject No	6
Reason	developed viral gastroenteritis (not related to study drug)
Period	prior to per II
Replacement	N

Subject No	7
Reason	elected to withdraw
Period	prior to per II
Replacement	N

Subject No 12
Reason dropped by clinical investigators due to flu-like symptoms (not related to study drug)
Period prior to per II
Replacement N

Was there a difference in side effects for the test versus the reference? no

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
headache, nausea	**1**	**1**
cough	**1**	
Total:	**2**	**1**

Comments: (*on adverse events)*: none

Was there a difference in protocol deviations for the test versus the reference? no

Table 4 Protocol Deviations

Comments: There were no protocol deviations reported.

Table 5 Assay Validation – Within Study

	oxybutynin	desethyloxybutynin
QC Conc. (ng/ml)	0.200, 2.00, 20.0	1.00, 10.0, 100
Inter day Precision (%CV)	8.6, 5.5, 5.8	7.2, 6.4, 4.0
Inter day Accuracy (%)	105, 107, 102	103, 102, 104
Cal. Standards Conc. (ng/ml)	1.00 - 125 (7 pts)	0.500 - 125 (7 pts)
Inter day Precision (%CV)	4.5 - 10.4	2.9 - 8.1
Inter day Accuracy (%)	94.0 - 105	97.2 - 105
Linearity (r^2)	$\geq$ 0.9918	$\geq$ 0.9952

Chromatograms: OK

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

SOP No.	Date of SOP	SOP Title
no number	**no date**	**no title - repeat analysis protocol was spelled out under the "repeat analyses" list**

Comments on repeat assays:

- SOPs were followed.
- Did recalculation of plasma concentrations change the study outcome? no
- Does the reviewer agree with the outcome of the repeat assays? yes
- Provide any other comments about repeat assays. The formal SOP for the repeat analyses was not provided; only the informal one noted above.

Comments on Within-Study Validation:

Conclusion: Analytical method is incomplete due to insufficient long-term stability data and omission of the formal SOP for repeat analyses.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 9 and Figure 1

oxybutynin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	(ngxhr)/ml	115	52	116	56	0.99
AUC∞	(ngxhr)/ml	122	51	123	54	0.99
Cmax	ng	6.54	70	6.63	59	0.99
Tmax	hr	12.4	50	12.9	52	0.96
T1/2	hr	15.4	60	15.2	43	1.01
kel	1/hr	0.055	40	0.052	35	1.06

desethyloxybutynin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	(ngxhr)/ml	396	46	416	46	0.95
AUC∞	(ngxhr)/ml	411	45	431	46	0.95
Cmax	ng	22.3	46	24.2	55	0.92
Tmax	hr	7.25	61	8.44	38	0.86
T1/2	hr	9.73	63	10.8	65	0.90
kel	1/hr	0.094	55	0.084	55	1.12

Table 8 Least Square Geometric Means and 90% Confidence Intervals

oxybutynin

Parameter	Test	Reference	T/R	90% CI
AUC0-t	99.9	99.2	101	90.4; 112
AUC∞	106	106	100	89.9; 112
Cmax	5.34	5.48	97.4	85.2; 112

desethyloxybutynin

Parameter	Test	Reference	T/R	90% CI
AUC0-t	355	374	94.9	86.1; 105
AUC∞	370	389	95.1	86.3; 105
Cmax	20.1	21.4	93.9	82.6; 106

Table 9 Additional Study Information

oxybutynin

Root mean square error, AUC0-t	0.3039	
Root mean square error, AUC∞	0.3072	
Root mean square error, Cmax	0.3812	
mean ratio AUC0-t/AUC∞	T =0.94	**R =0.94**
Range of values, ratio AUC0-t/AUC∞	T =0.64 - 0.99	**R =0.76 - 0.99**

desethyloxybutynin

Root mean square error, AUC0-t	0.2748	
Root mean square error, AUC∞	0.2784	
Root mean square error, Cmax	0.3546	
mean ratio AUC0-t/AUC∞	T =0.96	**R =0.96**
Range of values, ratio AUC0-t/AUC∞	T =0.80 - 0.99	**R =0.84 - 0.99**

Comments: (on pharmacokinetic analysis)

- kel and AUC∞ were determined for how many subjects. all for parent and metabolite
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr none for parent and metabolite
  b. first scheduled post-dose sampling time as Tmax none, except for subj #9 (trt A) and 20 (trt A) for the metabolite
  c. first measurable drug concentration as Cmax. none, except for subj #9 (trt A) and 20 (trtA) for the metabolite
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? yes for parent and metabolite
- Were there statistically significant sequence or period effects? no for parent and metabolite
- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%. yes for parent and metabolite
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A

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

Table 9 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Oxybutynin

PRODUCT=A:TEST

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	45	0.000	0.000	.		(b) (4)
C2	2.00 HR	45	1.128	2.297	203.620		
C3	4.00 HR	45	2.069	1.672	80.802		
C4	6.00 HR	45	3.468	2.323	66.961		
C5	8.00 HR	45	3.167	3.263	103.028		
C6	9.00 HR	45	3.812	4.022	105.495		
C7	10.00 HR	45	3.802	4.187	110.125		
C8	11.00 HR	45	4.676	4.265	91.199		
C9	12.00 HR	45	4.871	3.949	81.071		
C10	13.00 HR	45	3.884	2.939	75.669		
C11	14.00 HR	45	3.401	2.353	69.181		
C12	15.00 HR	45	3.596	2.390	66.469		
C13	16.00 HR	45	3.111	1.857	59.705		
C14	18.00 HR	45	2.195	1.396	63.579		
C15	20.00 HR	45	1.925	1.255	65.203		
C16	24.00 HR	45	2.943	2.237	76.018		
C17	30.00 HR	44	1.904	1.233	64.795		
C18	36.00 HR	44	1.316	1.094	83.107		
C19	48.00 HR	44	0.887	1.052	118.550		
C20	60.00 HR	44	0.394	0.396	100.537		
C21	72.00 HR	45	0.233	0.269	115.253		

PRODUCT=B:REF

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	45	0.000	0.000	.		(b) (4)
C2	2.00 HR	45	0.402	0.368	91.596		
C3	4.00 HR	45	2.414	1.582	65.520		
C4	6.00 HR	45	4.065	2.339	57.546		
C5	8.00 HR	45	4.001	2.798	69.934		
C6	9.00 HR	45	4.574	3.682	80.515		
C7	10.00 HR	45	4.372	3.366	76.996		
C8	11.00 HR	45	5.066	3.614	71.346		
C9	12.00 HR	45	5.009	3.368	67.241		
C10	13.00 HR	45	4.734	3.349	70.750		
C11	14.00 HR	45	4.335	2.890	66.651		
C12	15.00 HR	45	4.388	2.862	65.221		
C13	16.00 HR	45	3.804	2.208	58.042		
C14	18.00 HR	45	2.625	1.620	61.707		
C15	20.00 HR	45	2.188	1.380	63.071		
C16	24.00 HR	45	2.250	1.411	62.698		
C17	30.00 HR	45	1.650	1.045	63.341		
C18	36.00 HR	45	1.217	1.003	82.387		
C19	48.00 HR	45	0.744	0.702	94.353		
C20	60.00 HR	45	0.356	0.327	91.913		
C21	72.00 HR	45	0.236	0.246	104.413		

Desethyloxybutynin

PRODUCT=A:TEST

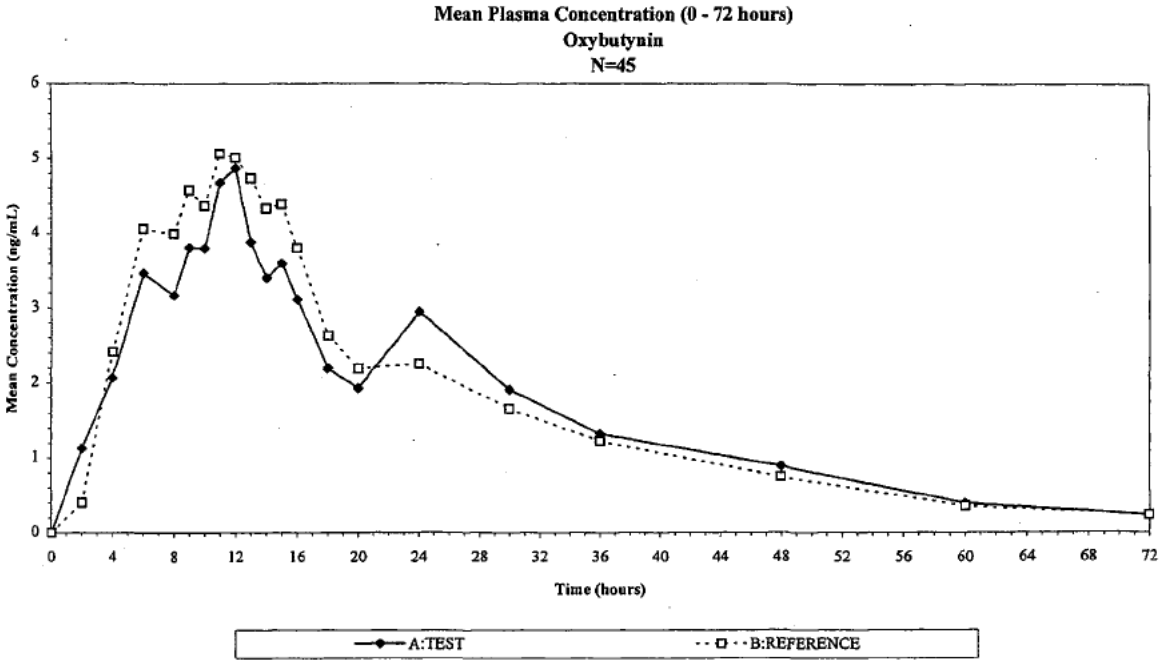
The MEANS Procedure

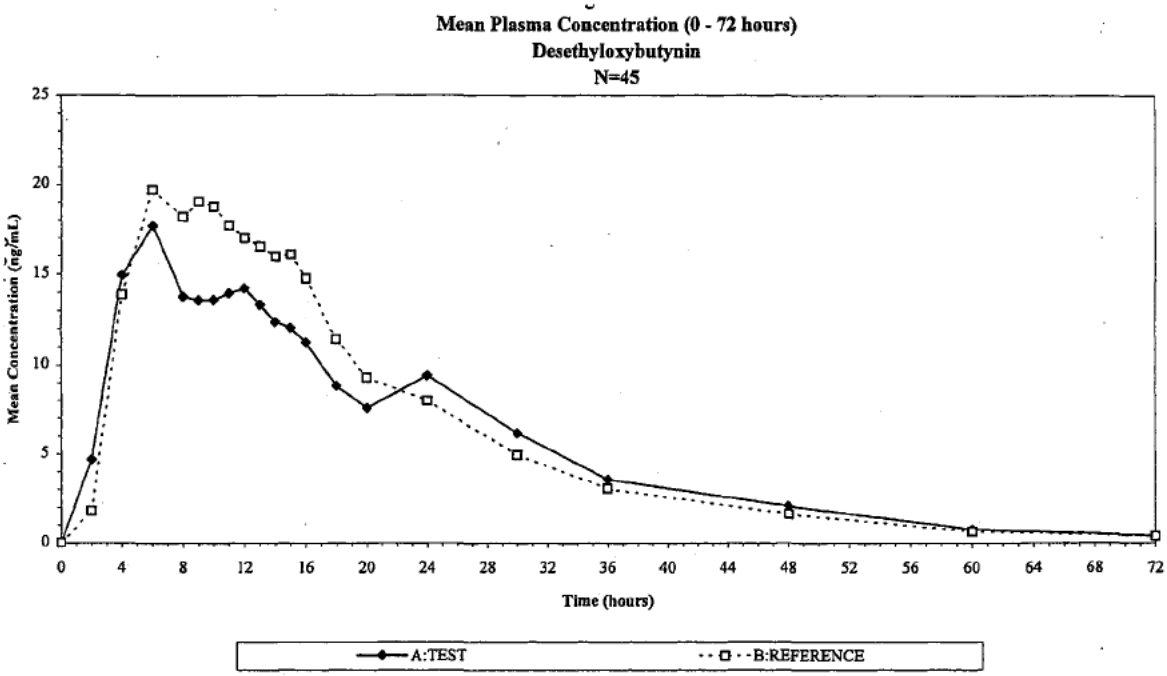
Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	45	0.000	0.000	.		(b) (4)
C2	2.00 HR	45	4.689	6.946	148.132		
C3	4.00 HR	45	14.960	9.829	65.702		
C4	6.00 HR	45	17.685	8.700	49.193		
C5	8.00 HR	45	13.773	7.984	57.968		
C6	9.00 HR	45	13.578	8.299	61.121		
C7	10.00 HR	45	13.600	9.612	70.678		
C8	11.00 HR	45	13.963	9.988	71.532		
C9	12.00 HR	45	14.228	9.484	66.657		
C10	13.00 HR	45	13.327	8.554	64.186		
C11	14.00 HR	45	12.382	7.972	64.379		
C12	15.00 HR	45	12.056	7.477	62.018		
C13	16.00 HR	45	11.247	6.565	58.368		
C14	18.00 HR	45	8.818	4.944	56.070		
C15	20.00 HR	45	7.576	4.501	59.418		
C16	24.00 HR	45	9.400	7.212	76.724		
C17	30.00 HR	44	6.167	4.253	68.956		
C18	36.00 HR	44	3.566	3.217	90.205		
C19	48.00 HR	44	2.084	3.044	146.060		
C20	60.00 HR	44	0.768	1.092	142.116		
C21	72.00 HR	45	0.400	0.619	154.536		

PRODUCT=B:REF

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	45	0.000	0.000	.		(b) (4)
C2	2.00 HR	45	1.804	1.388	76.926		
C3	4.00 HR	45	13.894	6.279	45.193		
C4	6.00 HR	45	19.715	9.159	46.456		
C5	8.00 HR	45	18.189	10.858	59.695		
C6	9.00 HR	45	19.045	12.650	66.424		
C7	10.00 HR	45	18.771	12.819	68.294		
C8	11.00 HR	45	17.706	10.027	56.631		
C9	12.00 HR	45	17.005	10.073	59.236		
C10	13.00 HR	45	16.518	9.843	59.587		
C11	14.00 HR	45	15.988	10.052	62.874		
C12	15.00 HR	45	16.094	10.115	62.849		
C13	16.00 HR	45	14.770	8.544	57.847		
C14	18.00 HR	45	11.416	6.171	54.057		
C15	20.00 HR	45	9.270	5.106	55.081		
C16	24.00 HR	45	8.004	4.596	57.422		
C17	30.00 HR	45	4.947	2.789	56.391		
C18	36.00 HR	45	3.060	2.173	71.006		
C19	48.00 HR	45	1.633	1.514	92.718		
C20	60.00 HR	45	0.648	0.759	117.186		
C21	72.00 HR	45	0.378	0.577	152.732		

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study





2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	RA2-200
Study Title	A Relative bioavailability study of 15 mg oxybutynin chloride extended release tablets under fed conditions.
Clinical Site	PRACS Institute, Ltd.; Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	per I - 15 Dec 02; per II - 5 Jan 03
Analytical Site	(b) (4)
Analytical Director	(b) (6), Ph.D.
Analysis Dates	23 Jan 03 - 10 Feb 03
Storage Period (no. of days from first sample to final analysis)	57 days

Treatment ID	A	B
Test or Reference	test	reference
Product Name	oxybutynin Cl ER tablet	**Ditropan XL® ER tablet**
Manufacturer	Impax Laboratories	**Alza Corporation**
Batch/Lot No.	R02043-100B	0117620
Manufacture Date	27 Nov 02	N/A
Expiration Date	N/A	Dec, 2003
Strength	15 mg	15 mg
Dosage Form	tablet	tablet
Batch Size	(b) (4) dosage units	N/A
Production Size	(b) (4) dosage units	N/A
Potency	97.7%	97.0%
Content Uniformity	97.6%	97.0%
Dose Administered	1 x 15 mg	1 x 15 mg
Route of Administration	oral	oral

No. of Sequences	**2**
No. of Periods	**2**
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB – subj #3, 5, 8, 9, 13, 14, 15, 17, 18, 22, 23, 25, 27, 29, 30 BA – subj #1, 2, 4, 6, 7, 10, 11, 12, 16, 19, 20, 21, 24, 26, 28
Blood Sampling Times	0 (pre-dose), 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 30, 36, 48, 60 and 72 hrs
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	centrifuge, decant plasma and store at -20°C
IRB Approval	y
Informed Consent	y
Subjects Demographics	See Table 1
Length of Fasting	overnight
Length of Confinement	1 day pre-dose until 24 hrs post-dose
Safety Monitoring	BP, pulse obtained at zero hr and at 12 and 24 hr

Table 10 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	97
Mean	29.4	Mean	173	18-40	77	Male	70	Afr. Amer.	
SD	12.9	SD	27	41-64	23	Female	30	Hispanic	3
Range	18-62	Range	112-217	65-75	0			Asian	
				>75				Others	

Study Results

Table 11 Dropout Information

Subject No	3
Reason	elected to withdraw
Period	prior to per II
Replacement	N

Was there a difference in side effects for the test versus the reference? There were a few more effects for the test product.

Table 12 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
headache, bodyache, stomachache	4	2
insomnia	1	0
Total:	5	2

Comments: *(on adverse events)*

Was there a difference in protocol deviations for the test versus the reference? no

Table 13 Protocol Deviations

There were no protocol deviations reported.

Comments: none

Table 14 Assay Validation – Within Study

	oxybutynin	desethyloxybutynin
QC Conc. (ng/ml)	1.00, 10.0, 100	1.00, 10.0, 100
Inter day Precision (%CV)	5.78 - 7.74%	5.83 - 7.38%
Inter day Accuracy (% Accuracy)	99.4 - 106%	98.2 - 104%
Cal. Standards Conc. (ng/ml)	0.500 - 125 (7 pts)	0.500 - 125 (7 pts)
Inter day Precision (%CV)	2.8 - 6.2%	3.2 - 5.7%
Inter day Accuracy (% Accuracy)	94.0 - 106%	94.0 - 112%
Linearity (r^2)	≥0.9968	≥0.9950

Chromatograms: OK

Table 15 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
no number	**no date**	**no title - repeat analysis protocol was spelled out under the "repeat analyses" list**

Comments on repeat assays.

- SOPs were followed.
- Did recalculation of plasma concentrations change the study outcome? no
- Does the reviewer agree with the outcome of the repeat assays? yes

- Provide any other comments about repeat assays. The sponsor did not appear to submit repeat analyses on desethyloxybutynin. Were there any? Also, the formal SOP for the repeat analyses was not provided; only the informal one noted above.

Comments on Within-Study Validation:

Conclusion: Analytical method is incomplete due to insufficient long-term stability data and omission of the formal SOP for repeat analyses.

Table 16 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 2

oxybutynin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	(ngxhr)/ml	97.1	63	88.9	53	1.09
AUC∞	(ngxhr)/ml	116	58	113	47	1.03
Cmax	ng	5.75	63	5.11	56	1.13
Tmax	hr	12.8	56	11.7	55	1.09
T1/2	hr	14.8	45	20.6	66	0.72
kel	1/hr	0.060	62	0.047	61	1.28

desethyloxybutynin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	(ngxhr)/ml	416	51	453	56	0.92
AUC∞	(ngxhr)/ml	434	52	471	55	0.92
Cmax	ng	28.8	51	28.5	51	1.01
Tmax	hr	12.0	51	9.83	40	1.09
T1/2	hr	9.76	38	13.3	85	1.22
kel	1/hr	0.083	46	0.074	50	1.12

Table 17 Geometric Means and 90% Confidence Intervals

oxybutynin

Parameter	Test	Reference	T/R	90% CI
AUC0-t	83.4	77.7	107	N/A*
AUC∞	101	99.8	101	**N/A***
Cmax	4.81	4.40	109	**N/A***

desethyloxybutynin

Parameter	Test	Reference	T/R	90% CI
AUC0-t	374	397	94	N/A*
AUC∞	391	415	94	N/A*
Cmax	25.5	25.4	100	N/A*

*Confidence intervals not calculated since the study was initiated prior to the issuance of the BA/BE Food Guidance

Table 18 Additional Study Information

oxybutynin

Root mean square error, AUC0-t	0.2461	
Root mean square error, AUC∞	0.2269	
Root mean square error, Cmax	0.3452	
mean ratio AUC0-t/AUC∞	T =0.84	**R =0.79**
Range of values, ratio AUC0-t/AUC∞	T =0.54 - 0.97	**R =0.56 - 0.93**

The sponsor used thirteen time points in the Ke regression for one subject (#12, trt A) whose **AUC0-t/AUC∞** was 0.54. Upon inspection of his graph, the reviewer would probably have determined his AUC∞ to be not accurately calculable. Dropping that subject's **AUC∞** data, however, would not impact the outcome of the study.

desethyloxybutynin

Root mean square error, AUC0-t	0.1891	
Root mean square error, AUC∞	0.1835	
Root mean square error, Cmax	0.2759	
mean ratio AUC0-t/AUC∞	T =0.96	**R =0.96**
Range of values, ratio AUC0-t/AUC∞	T =0.87 - 0.99	**R =0.78 - 0.99**

Comments: (on pharmacokinetic analysis)

- ke and AUC∞ were determined for how many subjects. all except for subj #16 (trt A, per II, parent) and #5 (trt B, per II, parent)
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, none for parent and metabolite
  b. first scheduled post-dose sampling time as Tmax, and none for parent and metabolite
  c. first measurable drug concentration as Cmax. none for parent and metabolite
- Did pharmacokinetic parameters and T/R ratios calculated by the reviewer agree with firm's calculations? yes for parent and metabolite
- Were there statistically significant sequence or period effects? no, except for Cmax (period, parent) and Cmax (sequence, metabolite)
- Are the T/R ratios for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%. Y

- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A

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

Table 19 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Oxybutynin

PRODUCT=A:TEST

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	29	0.000	0.000	.		(b) (4)
C2	2.00 HR	29	0.000	0.000	.		
C3	4.00 HR	29	0.476	1.144	240.580		
C4	6.00 HR	29	2.067	2.610	126.268		
C5	8.00 HR	29	1.497	1.625	108.561		
C6	9.00 HR	29	1.472	1.567	106.467		
C7	10.00 HR	29	1.379	1.366	99.047		
C8	11.00 HR	29	2.960	3.242	109.504		
C9	12.00 HR	29	3.623	3.340	92.177		
C10	13.00 HR	29	3.229	3.312	102.571		
C11	14.00 HR	29	2.864	2.751	96.022		
C12	15.00 HR	29	3.059	2.527	82.612		
C13	16.00 HR	29	2.622	1.914	73.001		
C14	18.00 HR	29	2.001	1.490	74.449		
C15	20.00 HR	29	1.946	1.573	80.830		
C16	24.00 HR	29	3.415	2.988	87.487		
C17	30.00 HR	29	2.250	1.553	69.009		
C18	36.00 HR	29	1.561	1.257	80.547		
C19	48.00 HR	29	0.868	0.750	86.343		
C20	60.00 HR	29	0.354	0.514	145.228		
C21	72.00 HR	29	0.230	0.414	179.901		

PRODUCT=B:REF

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	29	0.000	0.000	.		(b) (4)
C2	2.00 HR	29	0.156	0.287	183.987		
C3	4.00 HR	29	2.336	1.506	64.457		
C4	6.00 HR	29	3.652	2.048	56.082		
C5	8.00 HR	29	3.483	2.622	75.266		
C6	9.00 HR	29	3.213	2.003	62.322		
C7	10.00 HR	29	2.883	1.638	56.798		
C8	11.00 HR	29	3.903	2.407	61.662		
C9	12.00 HR	29	3.518	1.951	55.458		
C10	13.00 HR	29	3.058	1.544	50.493		
C11	14.00 HR	29	3.056	1.675	54.822		
C12	15.00 HR	29	3.593	2.344	65.246		
C13	16.00 HR	29	2.963	1.717	57.947		
C14	18.00 HR	29	2.079	1.065	51.226		
C15	20.00 HR	29	1.783	0.851	47.711		
C16	24.00 HR	29	1.898	1.066	56.133		
C17	30.00 HR	29	1.464	0.741	50.592		
C18	36.00 HR	29	0.916	0.546	59.650		
C19	48.00 HR	29	0.579	0.556	95.949		
C20	60.00 HR	27	0.298	0.434	145.439		
C21	72.00 HR	29	0.103	0.262	255.233		

Desethyloxybutynin

PRODUCT=A:TEST

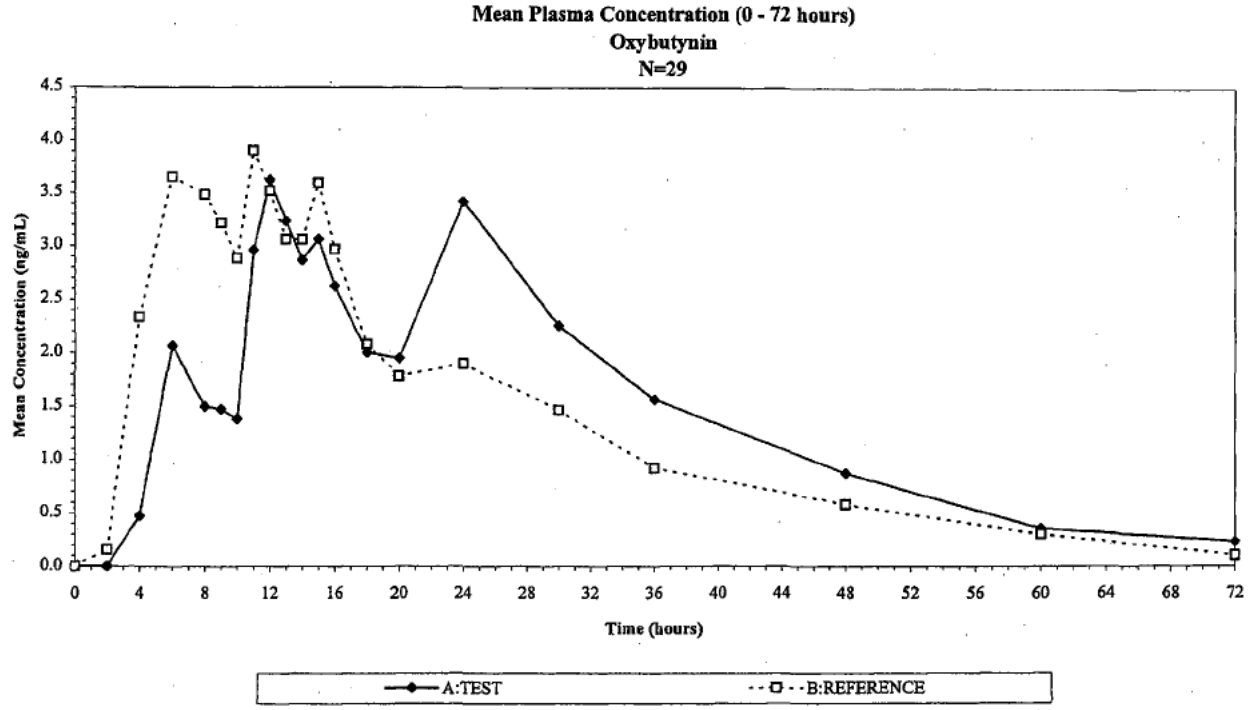
The MEANS Procedure

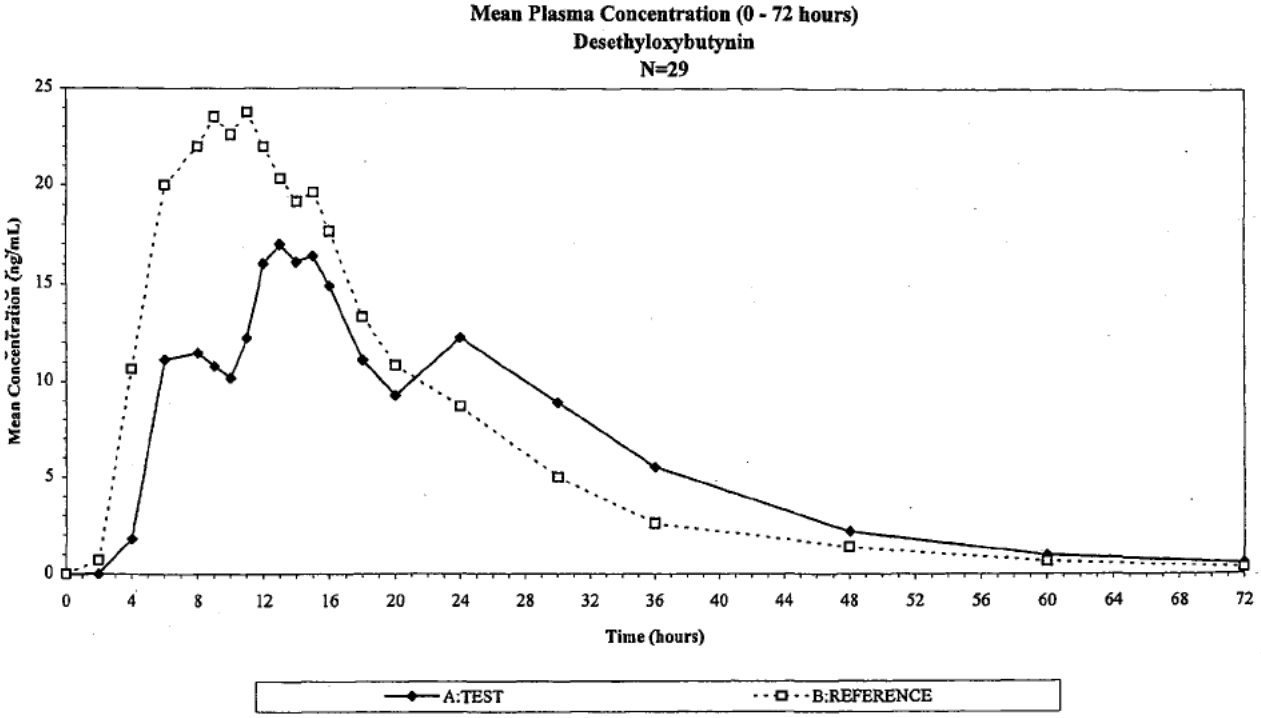
Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	29	0.000	0.000	.		(b) (4)
C2	2.00 HR	29	0.000	0.000	.		
C3	4.00 HR	29	1.807	4.796	265.378		
C4	6.00 HR	29	11.126	12.812	115.153		
C5	8.00 HR	29	11.451	11.764	102.734		
C6	9.00 HR	29	10.785	11.247	104.279		
C7	10.00 HR	29	10.184	9.937	97.571		
C8	11.00 HR	29	12.212	9.873	80.845		
C9	12.00 HR	29	16.011	12.344	77.098		
C10	13.00 HR	29	16.973	13.908	81.941		
C11	14.00 HR	29	16.101	14.016	87.050		
C12	15.00 HR	29	16.404	14.460	88.149		
C13	16.00 HR	29	14.891	12.382	83.148		
C14	18.00 HR	29	11.078	8.407	75.890		
C15	20.00 HR	29	9.261	6.848	73.939		
C16	24.00 HR	29	12.223	12.111	99.083		
C17	30.00 HR	29	8.891	7.308	82.191		
C18	36.00 HR	29	5.516	5.336	96.749		
C19	48.00 HR	29	2.199	2.284	103.850		
C20	60.00 HR	29	0.978	1.284	131.280		
C21	72.00 HR	29	0.566	0.900	159.026		

PRODUCT=B:REF

Variable	Label	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
C1	0.00 HR	29	0.000	0.000	.		(b) (4)
C2	2.00 HR	29	0.694	0.526	75.725		
C3	4.00 HR	29	10.641	4.996	46.955		
C4	6.00 HR	29	19.993	7.213	36.077		
C5	8.00 HR	29	22.019	11.982	54.419		
C6	9.00 HR	29	23.532	12.723	54.068		
C7	10.00 HR	29	22.623	13.189	58.296		
C8	11.00 HR	29	23.807	15.526	65.217		
C9	12.00 HR	29	21.986	14.256	64.840		
C10	13.00 HR	29	20.337	13.776	67.740		
C11	14.00 HR	29	19.165	12.378	64.584		
C12	15.00 HR	29	19.630	14.272	72.703		
C13	16.00 HR	29	17.658	13.166	74.560		
C14	18.00 HR	29	13.298	10.941	82.276		
C15	20.00 HR	29	10.811	8.562	79.195		
C16	24.00 HR	29	8.691	6.529	75.125		
C17	30.00 HR	29	4.992	3.069	61.476		
C18	36.00 HR	29	2.609	1.948	74.670		
C19	48.00 HR	29	1.384	1.157	83.630		
C20	60.00 HR	27	0.661	0.727	110.084		
C21	72.00 HR	29	0.346	0.548	158.204		

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





B. Formulation Data

INGREDIENT	5 mg per Tablet/ % per tablet	10 mg per Tablet/ % per tablet	15 mg per Tablet/ % per tablet
Oxybutynin chloride, USP	5.0mg/	10.0mg/	15.0mg/
Hypromellose, Type 2208, USP (b) (4)	(b) (4)		
Microcrystalline Cellulose (b) (4), NF			
Lactose Monohydrate NF			
Hydrogenated Vegetable Oil (b) (4), NF			
(b) (4)			
Methacrylic Acid Copolymer, (b) (4) NF			
Triethyl Citrate, NF			
Talc, USP			
(b) (4)			
Total	209 mg	209 mg	209 mg

(b) (4)

oxybutynin 15 mg - off-white, film coated, round, convex tablet, debossed with " (b) (4) (b) (4)

oxybutynin 10 mg - light pink, film coated, round, convex tablet, debossed with " (b) (4) (b) (4)

oxybutynin 5 mg - light purple, film coated, round, convex tablet, debossed with " (b) (4) (b) (4)

Ditropan XL® 15 mg - gray tablet imprinted with "15 XL"
Ditropan XL® 10 mg - pink tablet imprinted with "10 XL"
Ditropan XL® 5 mg - pale yellow tablet imprinted with "5 XL"

C. Dissolution Data

Table 1

Method Ref.:	sponsor's in-house	Medium:	phosphate buffer, pH 6.0 with 0.2% SLS
USP 27 Apparatus:	II	Volume:	900 mL
RPM:	100	Tolerance:	varied
No. Units Tested:	12	Assay Method:	HPLC
Reference Drug:	Ditropan XL® tablet		

Sampling Times (Hours)	Test Product: Lot No.: R02043 Strength: 15 mg			Ref Product: Lot No.: 0117620 Strength: 15 mg		
	Mean (%)	Range	SD	Mean (%)	Range	% CV
1	19	(b) (4)	2.0	0	(b) (4)	0
2	38		2.8	0		0.8
4	65		3.1	13		1.8
8	91		2.3	40		4.5
12	93		0.9	66		7.0

f_2= 20.11

Sampling Times (Hours)	Test Product: Lot No.: R02043 Strength: 15 mg			Ref Product: Lot No.: Strength:		
	Mean (%)	Range	SD	Mean (%)	Range	% CV
2	38	(b) (4)	3.0			
3	52		3.6			
4	64		4.0			
6	81		4.3			
8	91		3.4			

Sampling Times (Hours)	Test Product: Lot No.: R03013 Strength: 10 mg			Ref Product: Lot No.: Strength:		
	Mean (%)	Range	SD	Mean (%)	Range	% CV
2	38	(b) (4)	3.9			
3	53		4.7			
4	66		5.1			
6	84		4.8			
8	95		3.8			

Sampling Times (Hours)	Test Product: Lot No.: R03012 Strength: 5 mg			Ref Product: Lot No.: Strength:		
	Mean (%)	Range	SD	Mean (%)	Range	% CV
2	38	(b) (4)	5.9			
3	54		5.2			
4	66		5.3			
6	84		5.7			
8	90		6.0			

sponsor's proposed release specifications:

1 hr (b) (4)%
2 hr %
4 hr %
8 hr NLT (b) (4)%

D. Consult Reviews

N/A

E. SAS Output

fasted study

oxybutynin	 oxyfas.run
desethyloxybutynin	 doxyfas.run

fed study

oxybutynin	 oxyfed.run
desethyloxybutynin	 doxyfed.run

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-745 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Oxybutynin Cl ER tablets, 5, 10 and 15 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit long-term stability data that indicates the frozen samples are stable for the duration of the fasted study [from first administration to last sample analyzed - 74 days]. You have submitted stability data that shows long-term stability for only 53 days.

2. Please explain whether there were any sample repeat analyses for desethyloxybutynin in the fasted study. That table is missing from the study report.

   Please submit also the formal SOP governing Repeat Sample Analyses.

3. Please conduct additional dissolution testing as follows using the 15 mg test product bio-batch and a fresh batch of 15 mg Ditropan XL®, since the reference bio-batch has expired:

   a. 900 ml of water
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   b. 900 ml of acetate buffer, pH 4.5
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   c. 900 ml of 0.1N HCl
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   For methods a, b and c, a small amount of sodium lauryl sulfate may be added to facilitate dissolution if it can be shown to be necessary.

   d. 50 ml of simulated gastric fluid w/o enzyme
      apparatus VII (reciprocating disk)
      30 cycles/minute, 2-3 cm

Please sample at 1, 2, 4, 6, 8, 10 and 12 hrs or until at least 80% of the drug is released. Choose the best method and then conduct comparative dissolution testing with the 5 mg and 10 mg tablets vs the corresponding strength of the RLD using the best method. All raw data should be submitted with means at each sampling point, %CVs, minimum value and maximum value tabulated.

Sincerely yours,

Barbara M Davis

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-745
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ JLee E. S. 2/18/04
HFD-650/ Bio Team Leader
HFD-617/ Fabian-Fritsch
HFD-650/ Conner B MD 2/19/04

2/19/04

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Impax\ltrs&rev**76745N803.doc**

BIOEQUIVALENCY - DEFICIENCIES

1. **FASTING STUDY** (STF) 5/22/03 Strengths: 15 mg
Clinical: PRACS Inst. ✓ **Outcome: IC**
Analytical: (b) (4)

2. **FOOD STUDY** (STP) 5/22/03 Strengths: 15 mg
Clinical: same ✓ **Outcome: IC**
Analytical: same

7. **DISSOLUTION WAIVER** (DIW) 8/14/03 Strengths: 5 mg
✓ **Outcome: IC**

7. **DISSOLUTION WAIVER** (DIW) 8/14/03 Strengths: 10 mg
✓ **Outcome: IC**

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Bio-studies are incomplete due to analytical and dissolution deficiencies.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-745
Drug Product Name	oxybutynin Cl ER tablet
Strength	5, 10 and 15 mg
Applicant Name	Impax Laboratories, Inc.
Address	Hayward, California
Submission Date(s)	8 Dec 2004
Amendment Date(s)	
Reviewer	J. Lee
First Generic	yes
File Location	v:**firmsam\Impax**\ltrs&rev\76745A1204.doc

I. Executive Summary

This submission contains a correction to the accepted proposed dissolution method for the sponsor's test products. It also contains additional stability data for the three strengths of the test products using the accepted dissolution method. The dissolution data is acceptable. Previously, fasted and fed bio-studies were found acceptable. This amendment is acceptable.

In the previous review of this application, dated 19 May 04 and 17 Sept 04, DBE accepted the sponsor's proposed dissolution method for this drug product as follows:

900 ml of 0.1N HCl (with 0.2% SLS) for 2 hrs, apparatus II @ 50 rpm; then sample is switched to 900 ml of phosphate buffer (with 0.2% SLS), pH 6.0, apparatus II @ 50 rpm.

2 hr	NMT (b)(4)% dissolved
4 hr	(b)(4)%
6 hr	%
14 hr	NLT (b)(4)% dissolved

In this amendment, the sponsor is notifying DBE that we had misinterpreted the first stage of the dissolution method. It does not contain 0.2% SLS, only 0.1N HCl.

DBE acknowledges this correction.

The stability dissolution data is attached.

Comment:

1. The dissolution data is acceptable.

Recommendation:

1. The dissolution testing is acceptable. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXVII apparatus II (paddle) at 50 rpm for 2 hrs; then the sample is switched to 900 ml of phosphate buffer (with 0.2% SLS), pH 6.0, apparatus II @ 50 rpm. The test product should meet the following specification:

2 hr	NMT (b)(4)% dissolved
4 hr	(b)(4)%
6 hr	%
14 hr	NLT (b)(4)% dissolved

2. This amendment is acceptable.

R. Lee 1 Feb 05
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED GJPSingh
FT INITIALED GJPSingh Gurjaypal Singh 2-1-05

Concur: Dale P. Conner Date: 2/1/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/1-28-05

cc: ANDA #76-745 (original, duplicate), HFD-655 (Lee), Drug File, Division File

Method Ref.:	sponsor's proposed	Medium:	0.1N HCl (2 hrs); switch to pH 6.0 phosphate buffer w/0.2% SLS
USP 27 Apparatus:	II		
RPM:	50		
No. Units Tested:	12	Volume:	900 mL
Reference Drug:	Ditropan XL® tablet	Tolerance:	varies
		Assay Method:	HPLC

Sampling Times (hours)	Test Product: 12/5/04 tested Lot No.: R02043-100A Strength: 15 mg			Test Product: 12/6/04 tested Lot No.: R02043-100A Strength: 15 mg		
	Mean (%)	Range	%CV	Mean (%)	Range	%CV
2	0	(b) (4)	0	0	(b) (4)	0
4	28		5.0	26		9.1
6	52		3.3	49		6.4
14	92		1.3	90		2.8

Sampling Times (hours)	Test Product: 12/5/04 tested Lot No.: R03013 Strength: 10 mg			Test Product: 12/6/04 tested Lot No.: R03013 Strength: 10 mg		
	Mean (%)	Range	%CV	Mean (%)	Range	%CV
2	0	(b) (4)	0	0	(b) (4)	0
4	27		11.8	27		9.9
6	50		8.2	51		8.8
14	91		5.3	93		3.4

Sampling Times (hours)	Test Product: 12/5/04 tested Lot No.: R03012 Strength: 5 mg			Test Product: 12/6/04 tested Lot No.: R03012 Strength: 5 mg		
	Mean (%)	Range	%CV	Mean (%)	Range	%CV
2	0	(b) (4)	0	0	(b) (4)	0
4	28		6.7	26		4.4
6	50		5.8	48		8.8
14	94		2.9	90		3.4

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-745 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Oxybutynin Cl ER tablet; 15, 10 and 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge the correction in your proposed dissolution method and specification as follows:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP Apparatus II (paddle) at 50 rpm for the first two hrs; then switched to 900 mL of phosphate buffer (with 0.2% SLS), pH 6.0 at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> 2 hr NMT (b) (4)% dissolved
> 4 hr (b) (4)%
> 6 hr %
> 14 hr NLT (b) (4)% dissolved

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-745
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

v:\\firmsam\Impax\ltrs&rev\76745A1204.doc

Endorsements:
HFD-655/ Reviewer R.S. 1 Feb 05
HFD-655/ Bio team Leader CVSP 2-1-05
HFD-650/ D. Conner DPR 2/1/05

BIOEQUIVALENCE - ACCEPTABLE submission date: 8 Dec 04

4. **DISSOLUTION DATA** (DIS) All Strengths
Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Dissolution method correction noted. Stability data using DBE approved method is acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-745 SPONSOR : Impax Laboratories, Inc.

DRUG AND DOSAGE FORM : oxybutynin Cl ER tablet

STRENGTH(S) : 5, 10 and 15 mg

TYPES OF STUDIES : dissolution amendment

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S): N/A

DISSOLUTION : OK per sponsor's proposed method. Acknowledge correction in dissolution method. Stability data OK.

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic ___ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

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

DBE Dissolution Method and Spec acknowledged by firm: Yes _____Amendment Date_____

PROJECT MANAGER: _____ DATE:_____

PRIMARY REVIEWER : JLee BRANCH: II

INITIAL : R. S. DATE : 1 Feb 05

TEAM LEADER : GJPSingh BRANCH:

INITIAL : GJPS DATE : 2-1-05

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

INITIAL : DPC DATE : 2/1/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-745

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IMPAX LABORATORIES, INC.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 | Fax (510) 471-3200

May 22, 2003

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

Re: ANDA for Oxybutynin Chloride Extended-Release Tablets, 15 mg

Dear Mr. Buehler:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Laboratories, Inc hereby submits an Abbreviated New Drug Application (ANDA) for Oxybutynin Chloride Extended-Release Tablets, 15 mg. The reference listed drug, Ditropan XL® (oxybutynin chloride) tablets is the subject of Alza Pharmaceutical's approved NDA 20-897. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Laboratories, Inc. as the manufacturing site for the drug product. The submission contains 14 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in both Microsoft Word and PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the application.

One (1) write-protected diskette containing the pharmacokinetic data resulting from the bioequivalence studies is also included in the archival copy of this submission, in a plastic insert.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
MAY 23 2003
OGD / CDER

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 : June 2, 2003

TO : Director
Division of Bioequivalence (HFD-650)

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

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Oxybutynin Chloride Extended-release Tablets, 15 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

IMPAX Laboratories, Inc. has submitted ANDA 76-745 for Oxybutynin Chloride Extended-release Tablets, 15 mg . The ANDA contains a certification pursuant to 21 USC 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 IMPAX Laboratories, Inc. on May 22, 2003 for its Oxybutynin 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 First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 76745 **FIRM NAME IMPAX**

DRUG NAME oxybutynin Cl ER

DOSAGE FORM tablet
SUBJ: Request for examination of: Bioequivalence Study

Requested by: Martin Shimer Date: June 2, 2003
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:

R. Lee Date: 5 June 03
Reviewer

Team Leader Date: ~~6/5~~ 6/5/2003

Director, Division of Bioequivalence Date: 6/5/03

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	2	2	
Assay Methodology	☒	☐	1	1	
Procedure SOP	☒	☐	1	1	
Methods Validation	☒	☐	1	1	
Study Results Ln/Lin	☒	☐	2	2	
Adverse Events	☒	☐	2	2	
IRB Approval	☒	☐	2	2	
Dissolution Data	☒	☐	1	1	
Pre-screening of Patients	☒	☐	2	2	
Chromatograms	☒	☐	2	2	
Consent Forms	☒	☐	2	2	
Composition	☒	☐	1	1	
Summary of Study	☒	☐	2	2	
Individual Data & Graphs, Linear & Ln	☒	☐	2	2	
PK/PD Data Disk Submitted)	☒	☐	2	2	data files posted to EDR
Randomization Schedule	☒	☐	2	2	
Protocol Deviations	☒	☐	2	2	
Clinical Site	☒	☐	2	2	
Analytical Site	☒	☐	2	2	
Study Investigators	☒	☐	2	2	

Medical Records	☒	☐	2	2	
Clinical Raw Data	☒	☐	2	2	
Test Article Inventory	☒	☐	2	2	from drug dispensing logs
BIO Batch Size	☒	☐	1	1	
Assay of Active Content Drug	☒	☐	1	1	
Content Uniformity	☒	☐	1	1	
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐	2	2	
Statistics	☒	☐	2	2	
Summary results provided by the firm indicate studies pass BE criteria	☒	☐	2	2	
Waiver requests for other strengths / supporting data	☐	☐			N/A

Additional Comments regarding the ANDA:

This application contains a fasted and a fed bio-study. Both oxybutynin and metabolite, desethyloxybutynin, were measured in both studies.

Control docs #00-025 and 01-297 recommend that oxybutynin and desethyloxybutynin be measured. The metabolite is formed as a result of presystemic metabolism and is active.

IMPAX

Laboratories, Inc.

30831 Huntwood Avenue
Hayward, CA 94544
Tel. (510) 476-2018 Fax (510) 476-2091

FACSIMILE COVER SHEET

TO: Beth Fritsch, Regulatory Support Branch, OGD DATE: July 1, 2003

FAX NUMBER: 1-301-594-1174

TOTAL NUMBER OF PAGES (INCLUDING THIS COVER SHEET): 4

FROM: Mark C. Shaw PHONE NUMBER: 510-476-2018
Senior Director, Regulatory Affairs and Compliance

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets)

Dear Ms. Fritsch:

This correspondence follows your voice mail message today. I revised the FDA Form 356h that accompanied IMPAX's May 22, 2003 original ANDA submission as per your request.

The only changes made were to delete "USP" from the Established Name and to re-date and re-sign the form. I will send you the form bearing original signature under separate cover.

If you have questions or require any additional information, please contact me.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 16, 2003

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

Re: ANDA 76-745
Oxybutynin Chloride Extended-Release Tablets, 15 mg

Attn: Beth Fritsch (Regulatory Support Branch)

Dear Mr. Buehler:

This correspondence follows my July 15, 2003 telephone conversation with Ms. Beth Fritsch of your office regarding the above-referenced ANDA.

Ms. Fritsch requested that IMPAX Laboratories, Inc. (IMPAX) prepare a revised Market Exclusivity statement to reflect the recently granted New Patient Population (NPP) exclusivity and Pediatric Exclusivity extension (PED) granted to NDA 20-897. A revised Market Exclusivity statement accompanies this correspondence.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

ANDA 76-745

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

JUL 21 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.

Reference is made to the telephone conversations dated July 1, 2003 and July 15, 2003 and your correspondences dated July 1, 2003 and July 16, 2003.

NAME OF DRUG: Oxybutynin Chloride Extended-release Tablets, 15 mg

DATE OF APPLICATION: May 22, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 23, 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 B. Davis for

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

cc: ANDA 76-745
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 17JUL-2003 date
HFD-615/BFritsch, CSO 7/16/03 date
Word File
V:/FIRMSAM/Impax/ltrs&rev/76745.ack
FT/BFF 07/16/03
ANDA Acknowledgment Letter!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA#: 76-745 **FIRM NAME** IMPAX LABORATORIES INC.

RELATED APPLICATION(S): NA **First Generic Product Received?** YES

DRUG NAME: OXYBUTYNIN CHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS 15 MG

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

Labeling Reviewer: Catterson, Debbie Micro Review: NA Clinical Review: NA

Letter Date MAY 22, 2003	**Received Date** MAY 23, 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	(Not Applicable to Electronically Archived Submissions)
Archival and Review copies Field Copy Certification (Original Signature) YES, orig. sig.	(Not Applicable to Electronically Archived Submissions)
Cover Letter YES	**Table of Contents YES**
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completedfor ALL Original Applications)	Refer to the Part 3 Combination Algorithm

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: 11-22-2015 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES**	☒

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** (Mult Copies N/A for E-Submissions) 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 100, 500, 1000	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES, orig. sig. **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):** R02043 **5. Study Type:** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) YES FASTING AND FED ON 15 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted YES SENT TO CDR c. In-Vitro Dissolution YES Fasting - Cmax - 85.17 - 111.66 AUCt - 90.41 - 112.2 AUCi - 89.93 - 111.86 Fed - Point estimates are ok. Dosing for study December 15, 2002 through January 8, 2003 Cmax - 109.16 AUCt - 107.35 AUCi - 100.80	☒
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 b. Type II DMF authorization letters or synthesis ok, DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) ok, Lot# MM120102 d. Applicant certificate of analysis ok e. Testing specifications and data from drug product manufacturer(s) ok f. Spectra and chromatograms for reference standards and test samples 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 2. CGMP Certification YES, orig sig. 3. CFN numbers	☒

Sec. XVII	**Environmental Impact Analysis Statement** 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)	☒

Reviewing CSO/CST **Beth Fabian-Fritsch** **Date** **06/13/03** Beth Fabian-Fritsch	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: for Gregg Davis **Date:** 7/18/03	
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

Fed study for bioequivalence uses point estimates rather than confidance intervals. This is ok since dosing began before 1/31/03.

07/15/03 - Contacted firm to let them know about a NPP exclusivity.
07/16/03 - Firm revised their exclusivity statement to include the new exclusivity.

OGD Template Revised 04/04/2003

ANDA 76-745 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for gross errors in letter.

✓ 3) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 4) Check address and contact person on letter vs. 356(h).

✓ 5) Check for any t-cons and verify date and correspondence date.

✓ 6) Check Patent Certification information in entered in COMIS (by Margo) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 7) Check for any comments or problems raised by reviewer on Check List.

✓ 8) Sign Check List.

✓ 9) Check electronic Orange Book to verify current patent information.

✓ 10) Review 356 (h). Check NDA number and RLD for correct reference.

✓ 11) Review Basis for Submission.

✓ 12) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 13) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

Concurs Mowry Signed 14) Sign cover letter 505 (J)(2)(A) OK, date, and full signature.

✓ 15) Pull USP information. (USP ____yes ✓ no)

✓ 16) Final Grammar review on letter.

____ 17) EES slip.

____ 18) Document in record book.

Signature Lynnette M. Bruno date 7/18/03

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 14, 2003

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

NEW PRODUCT
STRENGTH AMENDMENT

ORIG AMENDMENT

Re: ANDA for Oxybutynin Chloride Extended-release Tablets, 15 mg
Addition of 5 mg and 10 mg strengths

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, IMPAX Laboratories, Inc hereby submits an amendment to Abbreviated New Drug Application (ANDA) 76-745 for Oxybutynin Chloride Extended-release Tablets, 15 mg. This amendment provides for the addition of 5 mg and 10 mg strengths. IMPAX recognizes that this amendment contains significant data under 21 CFR 314.96(a)(2), and that the submission of such data may extend the review time of the application up to 180 days.

A waiver of evidence of *in-vivo* bioequivalence for the 5 mg and 10 mg strengths of Oxybutynin Chloride Extended-release Tablets, 15 mg is provided in Section VI of this amendment.

Also included with this amendment is an electronic submission of the package insert word processor file, prepared in both Microsoft Word and PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the application.

This amendment contains 3 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

cc: Rochelle Young, SF-DO

RECEIVED
AUG 19 2003
OGD/CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 18, 2003

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

(NC)
NEW CORRESP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 15 mg)
Documentation of Paragraph IV Patent Notification and Receipt of Notice

Attn: Beth Fritsch (Regulatory Support Branch)

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for the above-referenced ANDA to the following parties and that the Notice met the content requirements specified in 21 CFR 314.95(c):

Alza Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210
U.S. Certified Mail tracking number: 7003-1010-0000-5209-8963
Return Receipt Date of Delivery: 07/29/03

As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed parties. A copy of the original U.S. Postal Service Return Receipt (showing proof of delivery) accompanies this letter.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
AUG 21 2003
OGD/CDER

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

NEW CORRESP
NC

September 8, 2003

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

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Documentation of Paragraph IV Patent Notification and Receipt of Notice

Attn: Beth Fritsch (Regulatory Support Branch)

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for the above-referenced ANDA to the following party and that the Notice met the content requirements specified in 21 CFR 314.95(c):

Patterson, Belknap, Webb & Tyler, LLP
1133 Avenue of the Americas
New York, NY 10036-6710
U.S. Certified Mail tracking number: 7003-1010-0000-5210-5449
Return Receipt Date of Delivery: 08/25/03

As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed parties. A copy of the original U.S. Postal Service Return Receipt (showing proof of delivery) accompanies this letter.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

New Strength

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA# 76-745 FIRM NAME IMPAX

RELATED APPLICATION(S) _____

DRUG NAME: Oxybutynin Chloride

DOSAGE FORM: Extended-release Tablets 15mg

FIRST GENERIC? NO

New Strength
5mg and 10mg
Added

Electronic Submission (Chem)_____ E-mail notification sent_____

Team Leader _____

Labeling Reviewer _____

Random Assignment _____

Micro Reviewer _____

Pharmacodynamic study (Dr. Fanning) _____

Team Leader: Dave Gill
Project Manager: Sarah Kim
RN: 4

Letter Date August 14, 2003 Received Date August 19, 2003

		YES	NO
	Comments EC-1+2=3 On Cards Yes Therapeutic Code 6050300 Relieve Voiding Symptoms/Neurogenic Bladder		
	Methods Validation Package (3 copies) NO (Required for Non-USP drugs)		✓
	Archival, and Review copies Field copy certification (original signature)	✓	
	Cover Letter	✓	
	Table of Contents	✓	

Sec.			
	Signed and Completed Application Form (356h) (Statement regarding (Rx) OTC Status) RX - Yes	✓	
Sec. II	Basis for Submission NDA# 20-897 RLD Ditropan Firm Alza Pharmaceuticals Is an ANDA suitability petition required?_____ If yes, consult needed for pediatric study requirement.	✓	
Sec. III	Patent Certification 1. Paragraph? IV 2. Expiration of Patent 11-22-2015 A. Pediatric Exclusivity Submitted?_____ B. Pediatric Exclusivity Tracking System checked?_____	✓	
	Exclusivity Statement yes	✓	
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use_____ 2. Active ingredients_____ 3. Route of administration_____ 4. Dosage Form_____ 5. Strength_____	✓	
Sec. V	Labeling How Supplied: 100, 500, 1000 1. 4 copies of draft (each strength and container) or 12 copies of FPL_____ 2. 1 RLD label and 1 RLD container label_____ 3. 1 side by side labeling comparison with all differences annotated and explained_____	✓	
Sec. VI	Bioavailability/Bioequivalence 1. Financial certification (Form FDA 3454)_____ and Disclosure statement (Form 3455)_____ (for BE studies only!) 2. In Vivo Study Protocol(s)_____ 3. In Vivo Study(ies)_____ 4. Computer Disk Submitted yes sent to CDR 5. Request for Waiver of In Vivo Study(ies) yes ON 5mg and 10mg 6. In Vitro Dissolution Data yes 7. Formulation Data Same? (Comparison of all Strengths)_____ (Ophthalmics, Otics, Externals, Parenterals) 5mg (RO 3012) 10mg (RO 3013) 8. Paragraph IV bio study acceptable for filing_____ 9. Lot numbers of products used in Bio-study_____ 10. DSI inspection request needed?_____ 1st Generic_____ 1st study for site_____ Other_____ E-mail notification to bio PMs sent_____	Waiver request ✓	

Sec. VII	Components and Composition Statements 1. Unit composition and batch formulation 2. Inactive ingredients as appropriate_____	✓
Sec. VIII	Raw Materials Controls 1. Active Ingredients a. Addresses of bulk manufacturers_____ ✓ DMF # (b) (4) b. Type II DMF authorization letters or synthesis_____ Found in original 15mg. c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s)_____ d. Applicant certificate of analysis_____ e. Testing specifications and data from drug product manufacturer(s)_____ f. Spectra and chromatograms for reference standards and test samples_____ g. CFN numbers_____ 2. Inactive Ingredients a. Source of inactive ingredients identified_____ Found in Original b. Testing specifications (including identification and characterization)_____ c. Suppliers' certificates of analysis (specifications and test results)_____ d. Applicant certificate of analysis_____	✓
Sec. IX	Description of Manufacturing Facility 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing_____ 2. CGMP Certification yes 3. CFN numbers_____	✓
Sec. X	Outside Firms Including Contract Testing Laboratories 1. Full Address_____ 2. Functions_____ 3. CGMP Certification/GLP_____ 4. CFN numbers_____	✓
Sec. XI	Manufacturing and Processing Instructions 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate)_____ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified_____ 3. If sterile product: Aseptic fill_____ / Terminal sterilization_____ 4. Filter validation (if aseptic fill)_____ 5. Reprocessing Statement	✓

5mg – (b) (4)
10mg –

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_____ 2. In-process Controls a. Sampling plans and test procedures_____ b. Specifications and data_____	✓	
Sec. XIII	Container 1. Summary of Container/Closure System (if new resin, provide data)_____ 2. Components Specification and Test Data (Type III DMF References)_____ 3. Packaging Configuration and Sizes_____ 4. Container/Closure Testing_____ 5. Source of supply and supplier's address_____	✓	
Sec. XIV	Controls for the Finished Dosage Form 1. Sampling Plans and Test Procedures_____ 2. Testing Specifications and Data_____ 3. Certificate of Analysis for Finished Dosage Form_____	✓	
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted_____ 2. Post Approval Commitments_____ 3. Expiration Dating Period_____ 4. Stability Data Submitted a. 3 month accelerated stability data_____ b. Batch numbers on Stability records the same as the test batch_____	✓	
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance_____ 2. Finished Dosage Form_____ 3. Same lot numbers_____	✓	
Sec. XVII	Environmental Impact Analysis Statement	✓	

5mg Lot #112

[redacted] (b) (4)

100's — [redacted] (b) (4)

1000's

10mg Lot # 1203013

[redacted] (b) (4)

100's = [redacted] (b) (4)

4000's =

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 3. List of Convictions statement (original signature)_____	✓	

Reviewing CSO/CST [signature] Date 9/9/03

Recommendation: FILE REFUSE to FILE

Supervisory Concurrence/Date [signature] 15 Sept 2003

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD_____ for consult

Type of consult:

Comments regarding the ANDA:

1. Need Quantitative + Qualitative breakdown of [redacted] (b) (4)

+ [redacted] (b) (4) ok PMP ✓

Revised 12/99 - v:\division\revsupp\regsupp\chklst

ANDA 76-745 (NSA) Final Check List for Branch Chief

N/A 1) Check letter date and stamp date of ANDA vs. drafted letter.

N/A 2) Check for any NC arriving post stamp date but prior to Reg. Review.

N/A 3) Check for gross errors in letter.

N/A 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

N/A 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

✓ 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD.

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission.

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ____yes ____no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Steiner date 15 Sept 2003

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 22, 2003

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

NEW CORRESP
NC

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to the Office of Generic Drug's July 21, 2003 letter documenting the acceptance for filing of the above-referenced ANDA. The letter requested that IMPAX notify your office in the event that litigation occurred within the 45-day period following notification of the NDA Holder and Patent Owner.

IMPAX hereby confirms that Alza Corporation initiated a lawsuit within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. Accordingly, IMPAX is enclosing with this correspondence a copy of the complaint filed September 4, 2003 in the United States District Court for the Northern District of California.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

Enclosure

RECEIVED
SEP 25 2003
OGD/CDER

MINOR AMENDMENT

NOV 13 2003

ANDA 76-745

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: Impax Laboratories, Inc. TEL: 510.476.2018

ATTN: Mark Shaw FAX: 510.476.2091

FROM: Craig Kiester PROJECT MANAGER: (301) 827-5765

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 22, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended-Release Tablets.

Reference is also made to your amendment(s) dated: August 14, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of 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. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

CK 11/12/03

NOV 13 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-745 APPLICANT: Impax Laboratories Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. We note your proposed specification for [redacted] (b) (4) as shown on their Certificate of Analysis.

2. We recommend the inclusion of a [redacted] (b) (4) test/specification for release and stability of these drug products.

3. The limits for [redacted] (b) (4) should be revised to correspond to the [redacted] (b) (4) We recommend that you [redacted] (b) (4) acceptance criteria for release testing for all strengths to agree more closely with your reported data.

4. We suggest that the [redacted] (b) (4)

5. [redacted] (b) (4)

6. The limits for [redacted] (b) (4) acceptance criteria for stability for all strengths to agree more closely with your reported data.

7. [redacted] (b) (4) does not meet the specification (Page 003623, Volume 1.13). Please explain.

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

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. Your labeling information is currently under review. Any deficiencies will be communicated to you under separate cover.

3. Please provide updated room temperature stability data from the ANDA exhibit batches.

4. We have noted that you intend to (b) (4) in consultation with the local district of the agency.

5. The firms referenced in your ANDA application relative to the manufacturing, packaging and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 29, 2003

MINOR AMENDMENT

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

ORIG AMENDMENT
N/AM

Attn: Craig Kiester

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter responds to your November 13, 2003, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX' response. As required to complete each response, additional data are provided as attachments in this submission.

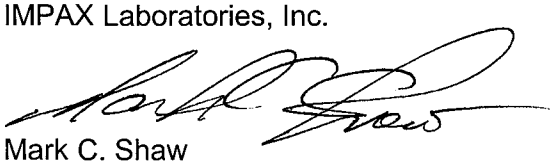
IMPAX notes and acknowledges the following:

- The bioequivalence and labeling information is under review and any deficiencies will be communicated under separate cover.
- (b) (4) in consultation with the local district of the agency.
- We acknowledge that a satisfactory cGMP evaluation is necessary for all firms involved in the manufacture of the drug product prior to approval of the ANDA.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 8**.

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.



Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

BIOEQUIVALENCY AMENDMENT

2-1

ANDA 76-745

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)

FEB 26 2004

APPLICANT: Impax Laboratories, Inc. TEL: 510-476-2018

ATTN: Mark Shaw FAX: 510-476-2091

FROM: Beth Fabian-Fritsch PROJECT MANAGER: (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on May 22, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended-release Tablets.

Reference is also made to your amendment(s) dated: August 14, 2003.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. 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:

FEB 26 2004

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-745 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Oxybutynin Cl ER tablets, 5, 10 and 15 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit long-term stability data that indicates the frozen samples are stable for the duration of the fasted study [from first administration to last sample analyzed - 74 days]. You have submitted stability data that shows long-term stability for only 53 days.

2. Please explain whether there were any sample repeat analyses for desethyloxybutynin in the fasted study. That table is missing from the study report.

   Please submit also the formal SOP governing Repeat Sample Analyses.

3. Please conduct additional dissolution testing as follows using the 15 mg test product bio-batch and a fresh batch of 15 mg Ditropan XL®, since the reference bio-batch has expired:

   a. 900 ml of water
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   b. 900 ml of acetate buffer, pH 4.5
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   c. 900 ml of 0.1N HCl
      apparatus I (basket) @ 100 rpm and
      apparatus II (paddle) @ 50 rpm

   For methods a, b and c, a small amount of sodium lauryl sulfate may be added to facilitate dissolution if it can be shown to be necessary.

   d. 50 ml of simulated gastric fluid w/o enzyme
      apparatus VII (reciprocating disk)
      30 cycles/minute, 2-3 cm

Please sample at 1, 2, 4, 6, 8, 10 and 12 hrs or until at least 80% of the drug is released. Choose the best method and then conduct comparative dissolution testing with the 5 mg and 10 mg tablets vs the corresponding strength of the RLD using the best method. All raw data should be submitted with means at each sampling point, %CVs, minimum value and maximum value tabulated.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3.1

IMPAX LABORATORIES, INC.

ORIGINAL

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

May 19, 2004

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

BIOEQUIVALENCE AMENDMENT

ORIG AMENDMENT
N/AB

Attn: Beth Fabian-Fritsch

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter responds to your February 26, 2004, facsimile, listing bioequivalence deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX' response. As required to complete each response, additional data are provided as attachments in this submission.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 14**.

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

RECEIVED
MAY 2 1 2004
OGD/CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 17, 2004

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0181)

NDA

Attn: Aaron Sigler

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter follows my September 2, 2004 telephone conversation with Aaron Sigler and Ginny Lee of your office, regarding IMPAX' May 19, 2004 Bioequivalence Amendment.

Each deficiency is listed in boldface type followed by IMPAX' response. As required to complete each response, additional data are provided as attachments in this submission.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 3.**

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

3.1

IMPAX LABORATORIES, INC.

ORIGINAL

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

November 12, 2004

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0181)

ORIG AMENDMENT
N/AM

Attn: Simon Eng

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter responds to the October 25 and 27, 2004 telephone messages from Simon Eng of your office, regarding the dissolution recommendations for this product made by the Division of Bioequivalence. Included with this amendment please find the following, updated to include the new dissolution specifications:

Attachment 1: Revised finished product specifications

Attachment 2: Revised stability protocol

Attachment 3: Revised drug release method and validation report

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 4**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

RECEIVED
NOV 17 2004
OGD / CDER

IMPAX LABORATORIES, INC.

ORIGINAL

4.1

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 6, 2004

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

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

Re: ANDA 76-745, Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, 15 mg

Attn: Simon Eng/John Grace

This letter responds to the August 13, 2004 e-mail correspondence from Debra Catterson of your office, listing revisions to the IMPAX Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, 15 mg container labeling and insert labeling. A copy of your correspondence accompanies this letter.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment are 12 copies of final printed insert labeling and container labels.

A complete copy of this labeling amendment, including specimens of the final printed labeling, is provided for the labeling reviewer in a separately labeled binder.

Also included with this amendment is an electronic submission of the package insert and container labels, prepared in PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
DEC 07 2004
OGD / CDER

IMPAX LABORATORIES, INC.

5.1

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 8, 2004

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0180)

ORIG AMENDMENT
N/AM

Attn: Simon Eng

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

Reference is made to FDA's October 25, 2004 facsimile correspondence confirming recommended *in-vitro* dissolution testing for the above-referenced drug product. FDA's correspondence followed IMPAX's May 19, 2004 Bioequivalence Amendment, which presented *in-vitro* dissolution test results for the drug product conducted under various test conditions.

IMPAX's May 19, 2004 amendment presented recommended dissolution conditions using 0.1N HCl for the first two hours followed by a switchover to pH 6.0 phosphate buffer, with 0.2% SLS for the remainder of the dissolution test. A description of these test conditions appears on page 10 of the May 19 amendment. Test results for both the brand and IMPAX product, obtained using these conditions, appear in Appendices 12 and 13.

The dissolution method recommended by IMPAX uses 0.2% SLS only in the pH 6.0 phosphate buffer following the switchover. The first two hours of the test are conducted only in 0.1N HCl. These conditions were recommended since the IMPAX formulation contains an enteric coating. The IMPAX product exhibits a "lag" during the first two hours, as also seen in the brand under these conditions, and then exhibits a first-order release profile that mimics the zero-order release profile of the brand.

FDA's October 25, 2004 correspondence agreed with the dissolution conditions recommended by IMPAX. However, FDA's recitation of the IMPAX conditions incorrectly stated that 0.2% SLS was to be added to both the 0.1N HCl (during the first two hours) and to the pH 6.0 phosphate buffer (following the switchover). The data upon which the recommended dissolution conditions were based used 0.2% SLS only following the switchover. In fact, it is inappropriate to add a surfactant as an aide to dissolution, especially since the dissolution of the product during the first two hours is to be limited to not more than 10% dissolved. FDA may have misinterpreted IMPAX's presentation of the data and concluded that SLS was present both before and after the switchover.

IMPAX's November 12, 2004 Telephone Amendment presented updated finished product specifications, a revised stability protocol, an updated drug release test method, and an updated validation report. Unfortunately, IMPAX incorporated the text from FDA's October 25, 2004 facsimile into the revised documents submitted on November 12, without realizing that 0.2% SLS was listed in the test conditions both before and after the switchover.

This oversight occurred because IMPAX concluded that FDA agreed with the IMPAX proposal and was merely reciting the agreed upon test conditions in FDA's October 25 facsimile correspondence. Accordingly, IMPAX revised its documentation to agree with the FDA text and failed to realize the incorporation of 0.2% SLS into the 0.1N HCl medium.

This oversight was IMPAX's, and we should have noted this discrepancy following receipt of your October 25 correspondence. IMPAX apologizes for not recognizing this discrepancy sooner. As a correction to the revised documents submitted November 12, please find the following, updated to include the correct dissolution conditions:

Attachment 1: Revised finished product specifications

Attachment 2: Revised stability protocol

Attachment 3: Revised drug release method and validation report

As requested in the November 29, 2004 telephone message from Simon Eng of your office, drug release data with the switchover drug release method has been generated using stability samples. Please refer to the data provided in **Attachment 4**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 5**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

RECORD OF TELEPHONE CONVERSATION/MEETING

Called Mark to request a [redacted] (b) (4) of the drug substance impurity specification for [redacted] (b) (4) from [redacted] (b) (4) to [redacted] (b) (4) in order to comply with ICH Q3A recommendations. I indicated that their data supports this request.

Mark though that this would not be a problem and he would fax us a telephone amendment asap if this would be acceptable to his company.

Mark thanked us for this update.

(end of memo)

File: V:\FIRMSAM\IMPAX\TELECONS\76745TCON.DOC

DATE:
December 16, 2004

ANDA NUMBER:
76-745

IND NUMBER:
N/A

TELECON

INITIATED BY:
- ☐ **APPLICANT/SPONSOR**
- ■ **FDA**

MADE:
- ■ **BY TELEPHONE**
- ☐ **IN PERSON**

PRODUCT NAME:
Oxybutynin Chloride ERT

FIRM NAME:
Impax Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Mark Shaw, Reg. Af.

TELEPHONE NUMBER:
(510) 517-1847 (cell ph.)

SIGNATURE:
12-16-04
A.J. Mueller

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 16, 2004

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0180)

ORIG AMENDMENT
N|AM

Attn: Simon Eng

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets,
5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter follows a December 16, 2004 telephone conversation with Dr. Albert Mueller of your office regarding the above-referenced ANDA. Dr. Mueller requested that IMPAX Laboratories, Inc. (IMPAX) revise its (b) (4) specification for (b) (4) from the current limit of (b) (4) to a revised limit of (b) (4) in order to comport with ICH Q3A (Impurities in New Drug Substances).

IMPAX has revised the specification as requested and has provided a copy in **Attachment 1**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

RECEIVED
DEC 2 1 2004
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT
N|AF

January 19, 2005

LABELING AMENDMENT

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

Re: ANDA 76-745, Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, 15 mg

Attn: Simon Eng/John Grace

This letter responds to the December 10, 2004 and January 4, 2005 e-mail correspondence from Postelle Birch of your office, listing revisions to the IMPAX Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, 15 mg container labeling and insert labeling. A copy of your correspondence accompanies this letter.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment are 12 copies of final printed insert labeling.

A complete copy of this labeling amendment, including specimens of the final printed labeling, is provided for the labeling reviewer in a separately labeled binder.

Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

for

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-745 Applicant IMPAX 5, 10, & 15mg

Drug Oxybutynin Chloride Extended-release tab Strength(s)

APPROVAL **TENTATIVE APPROVAL** **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** **OTHER**

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 9 Sept 2004 Initials MAS	Date 2/1/05 for Initials

Contains GDEA certification: Yes No (required if sub after 6/1/92)

Determ. of Involvement? Yes No

Pediatric Exclusivity System:
RLD = NDA# 20-897
Date Checked Previously granted.
Nothing Submitted
Written request issued
Study Submitted

Patent/Exclusivity Certification: Yes
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes No
Was applicant sued w/in 45 days: Yes No
Has case been settled: Yes No Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No (Not yet determined)
Date of latest Labeling Review/Approval Summary None in 1.1—31
Any filing status changes requiring addition Labeling Review Yes No
Type of Letter: Suscon-355 30month supp 2/25/06 for 5 & 10mg 11/29/06 for 15mg TA only
Comments:

2. Project Manager, Simin Eng Team 1 Review Support Branch	Date 9/9/04 Initials	Date Initials

Original Rec'd date 5/22/03
Date Acceptable for Filing 5/23/03 ✓
Patent Certification (type) IV
Date Patent/Exclus.expires Nov 22, 2011
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 9/15/03
Date of Office Bio Review 10/22/04
Date of Labeling Approv. Sum 8/~~18~~/2004
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 > N/A
MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted Rejected Pending N/A
Previously reviewed and tentatively approved Date N/A
Previously reviewed and CGMP def. /NA Minor issued Date N/A
Comments:

Modified-release dosage form: Yes No
Interim Dissol. Specs in AP Ltr: Yes

submitted prior to Aug 18, 03

3. David Read **(PP IVs Only)** Pre-MMA Language included OGD Regulatory Counsel, Post-MMA Language Included Comments: See Mylan's TA letter.	N/A	Date 1/28/05 Initials DR/R see copy inside folder. 1/28/05

4. Div. Dir./~~Deputy Dir.~~ Chemistry Div. I ~~II OR III~~ Comments:		Date 1/31/05 Initials RK

for TA, the CMC section is satisfactory ((b) (4) related issues will take months to resolve among OGD & ONDC. Therefore, it will be handled separately when a tentative approval is appropriate)

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. ANDA's for Mylan's drug product (76702/5mg and 76644/10mg) were tentatively approved on 1/12/05.

6. Vacant RLD= Ditropan XL Extended-release tablets NDA 20-897 (001 002 003)
Deputy Dir., DLPS 5mg, 10mg, 15mg Date_____
Initials_____
ALZA Corp.

7. Peter Rickman Date 2/1/05
Director, DLPS Initials (for West)
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable EES dated 9/15/04 (Verified 2/1/05). No O.A.I. alerts noted. Bioequivalence studies (fast-in and non-fasting) on the 15mg strength found acceptable. Dissolution studies on all 3 strengths also found acceptable. Waivers granted to the 5mg and 10mg strengths under 21 CFR 320.22(d)(2). Bio stud/test sites have acceptable OSI inspectional histories. Office-level bio endorsed 10/22/04. Labeling found acceptable 1/27/05. CMC found acceptable 1/28/05. Methods validation was not requested.

8. Robert L. West Date 2/1/2005
Deputy Director, OGD Initials (Robert West)
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: IVAX made paragraph 4 certifications to the '895, '754, '268, '355, and '115 patents. IVAX was sued for infringement only on the '355 patent. Litigation is ongoing - 30 month period expires 1/29/06 for the 15mg strength and 2/25/06 for the 5mg and 10mg strengths. Issues concerning 180-day exclusivity have not been addressed.
This ANDA is recommended for tentative approval.

9. Gary Buehler Date 2/1/05
Director, OGD Initials GB
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team Simon Eng Date 2/1
Review Support Branch Initials
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2/1 (2:25pm) Time notified of approval by phone (2:20pm) Time approval letter faxed
FDA Notification:
2/1 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/1 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Note: Initial submission of 5/22/03 only provided for the 15mg strength. The 5mg and 10mg strengths were added in the 8/14/03 amendment.

File V:/division/dlps/approvrou9.doc

Patent and Exclusivity Search Results from query on Appl No 020897 Product 001 in the OB_Rx list.

Patent Data

(and 002, 003)

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020897	001	5674895	MAY 22,2015			
020897	001	5674895*PED	NOV 22,2015			
020897	001	5840754	MAY 22,2015			
020897	001	5840754*PED	NOV 22,2015			
020897	001	5912268	MAY 22,2015			
020897	001	5912268*PED	NOV 22,2015			
020897	001	6124355	MAY 22,2015			U-378
020897	001	6124355*PED	NOV 22,2015			U-378
020897	001	6262115	MAY 22,2015			U-393
020897	001	6262115*PED	NOV 22,2015			U-393

PII

Based on the '355 patent

U-378, U-393: Method for treating urinary incontinence, Management of urinary incontinence etc.

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020897	001	NPP	APR 15,2006
020897	001	PED	OCT 15,2006

Addressed by Empax 7/1/05

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support

NAI
PIV Cert to '092.
7/26/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 19, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 19 2005
OGD/CDER

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

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 20, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

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

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 21, 2005

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

PATENT AMENDMENT

X P

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

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

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 22, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

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

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 25, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 25 2005
OGD / CDER

NAI PIV certification to patent '092
S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 26, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 26 2005
OGD / CDER

NAI PIV certification to patent '092
S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 27, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®. The patent cited in this amendment was listed in the electronic Orange Book.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 27 2005
OGD/CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw/GJ Boss Esq.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 0 2 2005
OGD / CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 3, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 4, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 0 4 2005
OGD / CDER

RECEIVED
AUG 0 4 2005
OGD / CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 5, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 8, 2005

PATENT AMENDMENT
X P

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

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 0 8 2005
OGD / CDER

IMPAX LABORATORIES, INC.

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

NI

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 9, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 10, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 11, 2005

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

PATENT AMENDMENT

M/XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 12, 2005

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

XP

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Documentation of Paragraph IV Patent Notification and Receipt of Notice

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for U.S. Patent 6,919,092 for the above-referenced ANDA to the following party and that the Notice met the content requirements specified in 21 CFR 314.95(c):

ALZA Corporation
1900 Charleston Road
Mountain View, CA 94043
Federal Express tracking number: 8482-6214-5101
Date of Delivery: 07/20/05

As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed parties. A copy of the FedEx signature proof of delivery accompanies this letter.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 12, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NI

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 15, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets,
5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 16, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 H[illegible], Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

N/4 NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

August 17, 2005

PATENT AMENDMENT

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

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

N/ NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 18, 2005

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

PATENT AMENDMENT

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 19, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 22, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 22 2005
OGD / CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 23, 2005

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

PATENT AMENDMENT

N/XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 24, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 ...nwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

August 25, 2005

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

PATENT AMENDMENT

AP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 25 2005
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

August 26, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 26 2005
OGD / CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 29, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 29 2005
OGD/CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 30, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 30 2005
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT

August 31, 2005

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

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

Attn: Simon Eng, Project Manager
Martin Shimer, Branch Chief, Regulatory Support Branch

Re: ANDA 76-745
Oxybutynin Chloride Extended-release Tablets, 5, 10, and 15 mg

Dear Mr. Buehler:

IMPAX Laboratories, Inc. (IMPAX) is in receipt of your February 1, 2005 Action Letter granting Tentative Approval to the above-referenced drug product. The purpose of this correspondence is to request final approval of ANDA 76-745. The section below entitled, "Patent and Legal," sets forth IMPAX's position regarding first-to-file exclusivity for the 15 mg strength following its Paragraph IV certification to U.S. Patent No. 6,124,355. Also addressed is the filing status for the subsequently listed U.S. Patent No. 6,919,092, and the extent to which that affects exclusivity for the 5 and 10 mg dosage strengths.

Final Printed Labeling

Final printed labeling was submitted in correspondence dated January 19, 2005.

CMC Changes

IMPAX hereby confirms that no CMC changes have been made to this application since issuance of FDA's February 1, 2005 Tentative Approval Letter.

Patent and Legal

U.S. Patent No. 6,124,355

IMPAX's May 22, 2003 Original ANDA for the 15 mg strength contained a Paragraph IV patent certification for the '355 patent. IMPAX submitted a Patent Amendment in correspondence dated August 18, 2003, documenting delivery of the Notice of Legal and Factual Basis of Noninfringement to Alza Corporation. The Notice was delivered on July 29, 2003.

RECEIVED
SEP 0 1 2005
OGD/CDER

Subsequently, litigation was brought against IMPAX in the United States District Court for the Northern District of California involving the '355 patent (Civil Action No. C-03-04032). The suit involved only the '355 patent, and none of the other patents to which IMPAX provided a Paragraph IV certification in its original ANDA (i.e., U.S. Patent Nos. 5,674,895; 5,840,754; 5,912,268; and 6,262,115).

Upon examining documents available to it, IMPAX believes that it was the first applicant to submit a substantially complete ANDA for the 15 mg strength containing a Paragraph IV patent certification to each listed patent. As such, IMPAX is entitled to a 180-day period of exclusivity with respect to the 15 mg strength.

IMPAX submitted a New Strength Amendment on August 14, 2003, providing for the addition of 5 mg and 10 mg strengths to ANDA 76-745. IMPAX's September 8, 2003 Patent Amendment documented delivery of the Notice of Legal and Factual Basis of Noninfringement on August 25, 2003. Civil Action No. C-03-04032 cited above covered all three product strengths.

U.S. Patent No. 6,919,092

The '092 patent was listed in Approved Drug Products with Therapeutic Equivalence Evaluations ('Orange Book') on July 19, 2005. IMPAX submitted its patent certification for the '092 patent, with respect to the 5, 10, and 15 mg strengths, on July 19, 2005 and simultaneously gave notice to the patent owner and NDA holder. As such, IMPAX was a "first-day filer" with respect to the '092 patent. IMPAX's August 12, 2005 Patent Amendment provided documentation of delivery of the Notice to Alza Corporation.

Certification to the '092 patent does not change IMPAX's first-filer status with respect to the 15 mg strength and the '355 patent, and cannot create a mutually-blocking exclusivity scenario with any other applicant. Therefore IMPAX retains sole 180-day exclusivity for the 15 mg strength. However, if IMPAX was the sole applicant to provide a first-day certification to the '092 patent it is then entitled to shared 180-day exclusivity for the 5mg and 10mg dosage strengths under FDA's patent-by-patent exclusivity rules.

Alza Corporation v. Mylan Laboratories et al (Civil Action No. 1:03CV61)

Reference is made to the above litigation involving Alza Corporation and Mylan Laboratories. This case was heard before the District Court for the Northern District of West Virginia. A decision in Alza v. Mylan is expected shortly.

IMPAX and Alza have entered into a stipulation whereby the decision of the West Virginia District Court relating to the validity (or invalidity) of the '355 patent will be binding on the parties. In other words, if the West Virginia Court finds that the '355 patent is invalid, this finding will also apply in Alza v. IMPAX (Civil Action No. C-03-04032) and judgment will be entered in favor of IMPAX. A copy of the court order is provided in **Attachment 1**.

Timing of Approval of IMPAX's ANDA 76-745

The effective date for approval of ANDA 76-745 is contingent upon several factors:

1. The 30-month stay of approval for IMPAX's 15 mg strength expires on January 30, 2006, whereas the stay applicable to the 5 mg and 10 mg strengths expires on February 26, 2006.

2. If the West Virginia Court in Alza v. Mylan finds that the '355 patent is invalid, IMPAX will be entitled to entry of judgment in its favor. IMPAX's ANDA will then be immediately eligible for final approval for at least the 15 mg strength.

3. If the West Virginia Court finds the '355 patent invalid and IMPAX was the only ANDA applicant to submit a Paragraph IV certification for '092 on the day the patent was listed, all strengths covered by IMPAX's ANDA will then be eligible for immediate final approval.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

Enclosure

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 31, 2005

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

PATENT AMENDMENT
XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 31 2005
OGD/CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 1, 2005

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

PATENT AMENDMENT

N/XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
SEP 01 2005
OGD/CDER

NAI patent '800 not listed in OB or dockets S. Middleton 9/13/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 2, 2005

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

PATENT AMENDMENT

XP

Re: ANDA 76-745 (Oxybutynin Cl Extended-Release Tablets, 5 mg, 10 mg, and 15 mg)
Patent Certification

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This action follows the listing by Alza Pharmaceutical of a new patent in the Orange Book for the Reference Listed Drug, Ditropan XL®.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 14, 2005

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

MC

Attn: Martin Shimer, Branch Chief, Regulatory Support Branch

Re: ANDA 76-745 (Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg)
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to IMPAX's August 12, 2005 Patent Amendment, which documented delivery of the Notice for U.S. Patent 6,919,092 ('092) to Alza Corporation.

IMPAX hereby confirms that Alza Corporation has not initiated a lawsuit on the '092 patent within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

October 12, 2005

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

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

ORIG AMENDMENT
N/Am

Attn: Simon Eng, Project Manager
Martin Shimer, Branch Chief, Regulatory Support Branch

Re: ANDA 76-745
Oxybutynin Chloride Extended-release Tablets, 5, 10, and 15 mg
Notice of Court Decision and Termination of 30-Month Stay

Dear Mr. Buehler:

Reference is made to IMPAX Laboratories, Inc.'s (IMPAX) August 31, 2005 letter requesting final approval of ANDA 76-745. The August 31 correspondence summarized the current status of this ANDA, which received tentative approval on February 1, 2005. The *Patent and Legal* section presented information regarding the status of litigation between IMPAX and Alza Corporation with respect to U.S. Patent Nos. 6,124,355 ('355) and 6,919,092 ('092).

The purpose of this correspondence is to update the Office of Generic Drugs regarding two related litigation events affecting the approvability of this ANDA and, as a result of those litigation outcomes, request immediate, final approval of the 15 mg strength of IMPAX's oxybutynin chloride extended-release tablets. As discussed in IMPAX's August 31 letter, immediate final approval of IMPAX's 5 mg and 10 mg strengths is dependent upon whether IMPAX was the only ANDA applicant to submit a Paragraph IV patent certification to the '092 patent on the day it was listed in the Orange Book.

IMPAX's previous confirmation regarding the status of Final Printed Labeling and CMC Changes remains unchanged and is summarized below. Presented under *Patent and Legal* is an update regarding two related litigation events affecting approvability of this ANDA.

IMPAX is also aware of an August 29, 2005 Citizen Petition submitted by Ortho-McNeil and assigned Docket No. 2005P-0352. The petition requests FDA to require ANDA applicants seeking approval of generic versions of Ditropan® XL to demonstrate bioequivalence of both the parent compound (oxybutynin) and active metabolite (desethyloxybutynin) in single-dose fasting and food-effect studies. IMPAX has reviewed the McNeil petition and believes that it has no merit and is merely an attempt to further delay the entry of generic versions of Ditropan® XL. IMPAX presents further comments below in the section entitled *Ortho-McNeil Citizen Petition.*

Final Printed Labeling

Final printed labeling was submitted in correspondence dated January 19, 2005.

CMC Changes

IMPAX hereby confirms that no CMC changes have been made to this application since issuance of FDA's February 1, 2005 Tentative Approval Letter.

Patent and Legal

Alza Corporation v. Mylan Laboratories et al (Civil Action No. 1:03CV61)

IMPAX's August 31, 2005 request for final approval made reference to litigation between Alza Corporation and Mylan Laboratories, the outcome of which would have a direct bearing on litigation between Alza Corporation and IMPAX.

As stated in our August 31 letter, IMPAX and Alza entered into a stipulation whereby the decision of the West Virginia District Court relating to the validity (or invalidity) of the '355 patent would be binding on the parties. In other words, if the West Virginia Court found the '355 patent invalid, this finding would also apply in Alza v. IMPAX (Civil Action No. C-03-04032) and judgment would be entered in favor of IMPAX. A copy of the court order is provided in **Attachment 1**. On September 27, 2005 the West Virginia District Court in Alza v. Mylan found the '355 patent invalid and entered judgment in favor of Mylan.

Alza Corporation v. IMPAX laboratories (Civil Action No. C 03-4032 VRW)

In accordance with the stipulation between IMPAX and Alza, IMPAX petitioned the Northern California District Court to enter judgment in favor of IMPAX based on the finding of invalidity of the '355 patent by the West Virginia Court. Provided in **Attachment 2** is a copy of the October 6, 2005 court order entering final judgment in favor of IMPAX. The effect of this ruling is to end the litigation between Alza and IMPAX as well as the 30-month stay of approval resulting from this litigation.

U.S. Patent No. 6,919,092

The '092 patent was listed in Approved Drug Products with Therapeutic Equivalence Evaluations ('Orange Book') on July 19, 2005. IMPAX submitted its patent certification for the '092 patent, with respect to the 5, 10, and 15 mg strengths, on July 19, 2005 and simultaneously gave notice to the patent owner and NDA holder. As such, IMPAX was a "first-day filer" with respect to the '092 patent. IMPAX's August 12, 2005 Patent Amendment provided documentation of delivery of the Notice to Alza Corporation.

Certification to the '092 patent does not change IMPAX's first-filer status with respect to the 15 mg strength and the '355 patent (now found invalid), and cannot create a mutually-blocking exclusivity scenario with any other applicant.

Therefore IMPAX retains sole 180-day exclusivity for the 15 mg strength. However, if IMPAX was the sole applicant to provide a first-day certification to the '092 patent it is then entitled to shared 180-day exclusivity for the 5mg and 10mg dosage strengths under FDA's patent-by-patent exclusivity rules.

Ortho-McNeil Citizen Petition

Reference is made to the August 29, 2005 Citizen Petition submitted to the Dockets Management Branch, FDA, by Ortho-McNeil. The Petition, assigned Docket No. 2005P-0352, requests FDA to require ANDA applicants seeking approval of generic versions of Ditropan® XL to demonstrate bioequivalence of both the parent compound (oxybutynin) and active metabolite (desethyloxybutynin) in single-dose fasting and food-effect studies and further, to require such applicants to demonstrate bioequivalence with respect to both the R- and S-enantiomers of the parent and active metabolite. IMPAX has reviewed the McNeil petition and believes that it has no merit and is merely an attempt to further delay the entry of generic versions of Ditropan® XL through an inappropriate use of the Citizen Petition process.

IMPAX is also aware of September 30, 2005 comments submitted to Docket No. 2005P-0352 by Mylan Pharmaceuticals, Inc. IMPAX has reviewed the Mylan comments and agrees with the comments set forth in their September 30 letter. As correctly stated by Mylan, FDA's guidance for industry on the conduct of bioequivalence studies recommends that ANDA applicants demonstrate bioequivalence for both the parent compound and active metabolite whenever there is evidence that the major metabolite is formed as the result of gut-wall or other pre-systemic metabolism, and that it contributes meaningfully to safety and/or efficacy[1].

In accordance with the General Considerations guidance, IMPAX conducted both single-dose fasting and food-effect studies of its 15 mg strength of oxybutynin chloride extended-release tablets versus Ditropan® XL Tablets, 15 mg and demonstrated bioequivalence for both the parent compound and active metabolite. Full reports from these studies were submitted in IMPAX's original ANDA submission, dated May 22, 2003. The statistical reports for the single-dose fasting and fed studies may be found, beginning on pages 1069 and 2704 respectively, of the original ANDA. These reports clearly establish that IMPAX demonstrated the bioequivalence of its ANDA formulation to that of DItropan® XL Tablets and met all FDA bioequivalence requirements in place at the time the studies were conducted. The Office of Generic Drugs subsequently issued a Tentative Approval letter for this ANDA on February 1, 2005.

IMPAX also concurs with comments submitted by Mylan with respect to demonstration of bioequivalence for R- and S-enantiomers of either the parent or metabolite.

---

[1] Guidance for Industry – Bioavailability and Bioequivalency Studies for Orally Administered Drug Products, General Considerations (October 2000).

FDA guidelines applicable at the time IMPAX conducted its studies, as well as now, establish four criteria, all of which must be present in order to require evaluation of enantiomeric isomers in bioequivalence studies:

1. the enantiomers exhibit different pharmacodynamic characteristics

2. the enantiomers exhibit different pharmacokinetic characteristics

3. primary efficacy and safety resides with the minor enantiomer; and

4. non-linear absorption is present, as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug, for at least one of the enantiomers

As was also noted by Mylan, Ortho-McNeil has provided no evidence that non-linear absorption is present. Indeed, Ortho-McNeil's own professional prescribing information for Ditropan® XL states that the "[p]armacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5 to 20 mg of Ditropan® XL are dose proportional." (emphasis added) Thus, by its own admission the fourth condition presented above is not satisfied and, as a result, there is no basis for requiring the measurement of the R- and S-enantiomers in any bioequivalence study between a test product of oxybutynin chloride extended-release tablets and Ditropan® XL.

The Summary Basis of Approval for Ditropan® XL is also noteworthy in that it cites comments by the FDA reviewer that the "R/S ratio of oxybutynin and desethyloxybutynin were not significantly different between Ditropan XL and oxybutynin IR[2]." In other words, consistent with the fact that oxybutynin exhibits linear pharmacokinetics, ER and IR formulations of oxybutynin yield similar R/S ratios for both the parent and metabolite, even between formulations with different absorption profiles (i.e., T_{max} and C_{max}). This again lends further support that Ortho-McNeil has introduced no new facts in its Citizen Petition that are not already known to FDA and that would affect the approvability of IMPAX's ANDA.

The timing of Ortho-McNeil's Citizen Petition is also highly suspect, and not the first time it has utilized such tactics merely to create administrative hurdles that only serve to further delay the approval of bioequivalent versions of Ditropan® XL Tablets and other drug products for which it has also inappropriately used the Citizen Petition process.

As this petition is suspect both to timing and merit, FDA should take immediate action to grant final approval to IMPAX's ANDA and should do so regardless of its ultimate decision with respect to the Ortho-McNeil petition.

---

[2] Summary Basis of Approval, Clinical Pharmacology and Biopharmaceutics Review, p. 14.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

Enclosure

Eng, Simon

From: Grace, John F
Sent: Thursday, December 15, 2005 4:04 PM
To: Birch, Postelle; Eng, Simon
Subject: RE: 76745/IMPAX/Oxybutynin Chloride Extended-release Tabs, 5mg 10mg and 15mg Labeling sign-off

I concur

-----Original Message-----
From: Birch, Postelle
Sent: Thursday, December 15, 2005 4:02 PM
To: Eng, Simon; Grace, John F
Subject: RE: 76745/IMPAX/Oxybutynin Chloride Extended-release Tabs, 5mg 10mg and 15mg Labeling sign-off

The approval summary signed by John Grace on January 28, 2005 is 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

-----Original Message-----
From: Eng, Simon
Sent: Thursday, December 15, 2005 2:28 PM
To: Birch, Postelle; Grace, John F
Subject: 76745/IMPAX/Oxybutynin Chloride Extended-release Tabs, 5mg 10mg and 15mg Labeling sign-off

Hi Postelle and John,
Please review and sign off.
Thanks,
S

Simon Eng
Project Manager, OGD, FDA
7500 Standish Place, MPN-II, HFD-617
Rockville, MD 20855
301-827-5765

ORIGINAL

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

January 12, 2006

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0180)

ORIG AMENDMENT
N/AM

Attn: Simon Eng

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter follows a January 5, 2006 telephone conversation with Simon Eng of your office regarding the above-referenced ANDA. Mr. Eng requested that IMPAX Laboratories, Inc. (IMPAX) revise its Oxybutynin Chloride active ingredient specifications to comport with those listed in the current USP.

IMPAX has reviewed the specifications for oxybutynin chloride active ingredient versus the USP monograph and has updated the specifications accordingly. The IMPAX test method for (b) (4) has been removed, and replaced with the USP method. In addition, the test has been renamed "Related Compounds", as listed in the current USP. Please find the revised specification in **Attachment 1**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JAN 17 2006
OGD / CDER

cc: Rochelle Young, SFDO

RECORD OF TELEPHONE CONVERSATION

FDA: The firm was contacted to clarify the discrepancy about the impurity limits for the drug substance Oxybutynin chloride.

The individual limits for (b) (4) The firm was asked to make the (b) (4)

The firm will get back to us tomorrow or day after tomorrow.

~~Firm: Yes.~~

End of the T-CON

DATE: 1/18/06

ANDA NUMBER: 76-745

PRODUCT NAME: Oxybutynin Tabs

INITIATED BY:

FIRM __ FDA _x

FIRM NAME:
Impax

FIRM REPRESENTATIVE:
Michelle Anderson

TELEPHONE NUMBER:

510-476-2010

FDA REPRESENTATIVE:
Yusuf Amin 1/18/06.
S. Eng 1.18.06

SIGNATURE

CC: ANDA 76745
DIVISION FILE
Chem Div I, T-con Notebook

Location: V:\FIRMSAM\IMPAX\TELECONS\76745.tcon.1.18.06.doc

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

January 23, 2006

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

TELEPHONE AMENDMENT
(Via Fax 301-594-0180)

ORIGINAL
N/HM

Attn: Simon Eng

Re: ANDA 76-745: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

Dear Mr. Buehler:

This letter follows a January 18, 2006 telephone conversation between the review chemist and Simon Eng of your office and Michele Anderson of IMPAX, regarding the January 12, 2006 telephone amendment for the above-referenced ANDA. Mr. Eng and the chemist requested that IMPAX Laboratories, Inc. (IMPAX) revise the (b) (4) (b) (4) limits in the oxybutynin chloride active ingredient in one of the two following ways:

1) Revise the limit for (b) (4)

2) Revise the limit for (b) (4)

IMPAX has reviewed its data collected to date and has opted to revise the limits as listed in #2 above. In addition, the limits for (b) (4) in concordance with those adopted by the supplier, as follows:

(b) (4) Previous Limit	New Limit
(b) (4)	

Please find the revised specification in **Attachment 1**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2**.

RECEIVED
JAN 25 2006
CGD / CDER

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

West, Robert L

From: West, Robert L
Sent: Wednesday, August 30, 2006 10:44 AM
To: Eng, Simon
Subject: ANDA 76-745 for IMPAX's Oxybutynin Chloride Extended-release Tablets

Simon:

I'm going through the approval/tentative approval package for IMPAX's ANDA 76-745 for Oxybutynin Chloride Extended-release Tablets 5 mg, 10 mg, and 15 mg. We propose to grant final approval to IMPAX's 15 mg strength (and continue the T/A for the 5 mg and 10 mg strengths).

There is an e-mail in the package from Postelle and John dated 12/15/05 stating that "the approval summary signed off by John Grace on January 28, 2005 is still acceptable for approval." Please confirm with the labeling team that the labeling is still acceptable for approval of the 15 mg strength.

Thanks,

Bob

A11.1

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

XP

August 31, 2006

PATENT AMENDMENT

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

Attn: Robert West

Re: ANDA 76-745
Oxybutynin Chloride Extended-release Tablets, 5, 10, and 15 mg
Consolidation of Appeals

Dear Mr. Buehler:

Reference is made to Mr. West's telephone inquiry on August 30, 2006, requesting an update on the status of legal proceedings between Alza and IMPAX. As discussed during the subsequent August 31, 2006 telephone conversation between the undersigned and Mr. West on August 31, 2006, the Alza v. Mylan appeal and the Alza v. IMPAX appeal have been consolidated into one case. Please refer to the Federal Circuit judge's ruling dated November 22, 2005 which is appended to this letter.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

Enclosure

Eng, Simon

From: Grace, John F
Sent: Tuesday, September 05, 2006 12:00 PM
To: Birch, Postelle; Eng, Simon
Subject: RE: 76745/Impax/Oxybutynin/Labeling Sign-off

I concur

76-745
Oxybutynin
Impax

9/5/06

-----Original Message-----
From: Birch, Postelle
Sent: Tuesday, September 05, 2006 11:25 AM
To: Eng, Simon
Cc: Grace, John F
Subject: RE: 76745/Impax/Oxybutynin/Labeling Sign-off

The approval summary is 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

-----Original Message-----
From: Eng, Simon
Sent: Tuesday, September 05, 2006 8:52 AM
To: Birch, Postelle
Cc: Grace, John F
Subject: 76745/Impax/Oxybutynin/Labeling Sign-off

Hi Postelle,

There is an e-mail in the Ap and TA package from you and John dated 12/15/05 stating that "the approval summary signed off by John Grace on January 28, 2005 is still acceptable for approval." Please confirm that the labeling is still acceptable for approval of the 15 mg strength.

Thanks,

Simon

Simon Eng
Project Manager, OGD, FDA
7500 Standish Place, MPN-II, HFD-617
Rockville, MD 20855
Phone # 301-827-5765
Fax # 301-594-0180
Email Address: simon.eng@fda.hhs.gov

West, Robert L

From: Birch, Postelle
Sent: Monday, September 11, 2006 3:03 PM
To: West, Robert L
Subject: RE: Ditropan XL

Great. I've already sent out an email to John and Jeanne confirming the last AP summary is 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: West, Robert L
Sent: Monday, September 11, 2006 3:02 PM
To: Birch, Postelle; Skanchy, Jeanne
Cc: Grace, John F
Subject: RE: Ditropan XL

Postelle:

Please confirm that we should be O.K. as long as we can approve TEVA's and IMPAX's ANDAs before October 15th using the current labeling. I think that we will be approving before October 15th as the C.P. is on the top of the priority list.

Thanks,

Bob

From: Birch, Postelle
Sent: Monday, September 11, 2006 2:57 PM
To: Skanchy, Jeanne
Cc: West, Robert L; Grace, John F
Subject: Ditropan XL

FYI

Please note that the pediatric exclusivity for Ditropan XL 20-897 (Oxybutynin extended release) expires on October 15, 2006. This directly affects ANDAs 76-644 and 76-702 for which BPCA language was substituted in the most recently submitted labeling.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020897	001	NPP	APR 15,2006
020897	001	PED	OCT 15,2006

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

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 11/9/2006
Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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 M Hirsch 11/3/06

George Benson, M.D.
Medical Team Leader, DRUP GS Benson 11/3/06

From: Marcea Whitaker, M.D.
Medical Officer, DRUP MB Whitaker 11/2/06

Ortiz, Stephan, R.Ph., Ph.D.
Clinical Pharmacologist, OCPB SR Ortiz 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.

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

/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

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: November 9, 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 76-745

Impax submitted ANDA 76-745 for oxybutynin ER tablet products, 5, 10, and 15 mg. Impax conducted both fed and fasting BE studies to demonstrate that its product was bioequivalent to Ditropan XL.

For Impax's fasting BE study submitted to ANDA 76-745, 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 study submitted to ANDA 76-745.

For Impax's fed BE study submitted to ANDA 76-745, 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 interval BE limits were not applied). Impax's fed BE study met these criteria; the point estimates for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 1.07, 1.01, and 1.09, respectively. The generic drug industry was aware that OGD used point estimate

[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.

acceptance criteria when 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%). 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 as bioequivalent. 21 CFR 320.25.

Both the AUC and C_{max} point estimates for Impax's fed BE study, which was 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 without calculating the 90% confidence intervals for AUC and C_{max}.

The studies for Impax'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). It is not known whether the 90% confidence intervals for the AUC and C_{max} geometric mean test/reference ratios from the fed BE study would have met the BE acceptance limits of 80 to 125%. However, 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, Impax enrolled only 30 subjects in its fed BE study, whereas its fasted BE study, in which the 90% confidence intervals met BE limits, enrolled 48 subjects.

---

[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)).

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.[5] 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 Impax'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 Impax to conduct the fed BE studies again. Impax'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 Impax's product would not be bioequivalent to Ditropan XL.

[5] The FDA-approved Ditropan XL package insert states that adult patients can be treated with doses ranging from 5 to 30 mg/day.

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

/s/

Barbara Davit
11/9/2006 04:17:09 PM
BIOPHARMACEUTICS

Dale Conner
11/13/2006 04:57:18 PM
BIOPHARMACEUTICS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-745 Applicant IMPAX Labs, Inc.
Drug Oxybutynin Chloride ER-release Tabs Strength(s) 5, 10, 15 mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer — Date 16 Dec 2005 — Date 8/30/06
Chief, Reg. Support Branch — Initials — Initials

Contains GDEA certification: Yes No (required if sub after 6/1/92)
Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA#
Date Checked
Nothing Submitted
Written request issued
Study Submitted

Patent/Exclusivity Certification: Yes No
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes No
Was applicant sued w/in 45 days: Yes No
Has case been settled: Yes No Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No Eligible only on 15mg strength
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes No
Type of Letter: Eligible for full approval on 15 mg strength only SPLIT AP
Comments: Eligible for TA on 5 & 10 mg strength d/t to Mylan 180 — Full for 15, TA for 5 & 10

2. Project Manager, Simon Team 1 — Date 12/15/05 — Date
Review Support Branch — Initials — Initials

Original Rec'd date 5/22/03
Date Acceptable for Filing 5/23/03
Patent Certification (type) IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)
First Generic Yes No — 7/1655 Regular strength approved before
15 mg new strength
5, 10 mg 1st Generic for extended-release

EER Status Pending Acceptable OAI
Date of EER Status FUR
Date of Office Bio Review 10/22/04, 2/1/05
Date of Labeling Approv. Sum 1/28/05
Labeling Acceptable Email Rec'd Yes No
Labeling Acceptable Email Filed Yes No
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes No
MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved TA'ed Date 2/1/05
Previously reviewed and CGMP def. /NA Minor issued Date N/A
Comments:

Modified-release dosage form: Yes No
Interim Dissol. Specs in AP Ltr: Yes

3. David Read (PP IVs Only) Pre-MMA Language included ✓ — Date 12/21/05
OGD Regulatory Counsel, Post-MMA Language Included — Initials
Comments: see revised version

4. Div. Dir./Deputy Dir. — Date 1/27/06
Chemistry Div. I II OR III — Initials
Comments:

CMC OK

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A This ANDA was previously tentatively approved on 2/1/05. Hylan's ANDA's 76-644 and 76-702 have also been tentatively approved.
5mg, 10mg, 15mg

6. Vacant RLD-Ditropan XL Extended-release Tablets Date_____
Deputy Dir., DLPS NDA 20-897 (001, 002, 003) Initials_____
ALZA Corp

7. Peter Rickman Date 8/30/06
Director, DLPS Initials Recused for
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: This ANDA was tentatively approved on 2/1/05. Refer to the administrative sign-off form completed at that time. On 8/31/05, IMPAX submitted a minor amendment to request final approval for the 15mg tablet strength based upon "first-to-file" status. Additional amendments addressing the legal status and minor CMC updates have also been submitted by IMPAX. CMC found acceptable 11/25/06. Methods validation was not requested. EES remains acceptable for approval per J. Grace email dated 12/15/05 (as endorsed 9/15/06).
EES verified 11/7/2006/RW

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes / No ; Petition: Yes No
Comments: Acceptable EES dated 4/18/06 (Noted 8/30/06) NDAT alerts noted - Impax made program 4 certifications to each of the patents listed in the "Orange Book" ('895, '754, '268, '355, '115 and '092). IMPAX was only sued on the '355 patent. The '355 patent was found invalid in a related case (ALZA vs. Hylan on 9/21/05). A court-ordered consented judgment was entered in favor of Impax in accordance with a prior stipulation between ALZA and Impax. Final approval of IMPAX's 5mg and 10mg strengths is currently blocked by Hylan's eligibility for 180-day generic drug exclusivity.

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments: Recommend Approve - 15mg strength
First Generic Approval PD or Clinical or BE Special Statement for Reg.Issue
TA - (2nd) for 5mg and 10mg strengths

10. Project Manager, Team Simon Date 11/13/06
Review Support Branch Initials
Bob called 11/9 4:10pm
_____ Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
_____ Time notified of approval by phone 16:18 pm by Bob on 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.
Note: Impax's original ANDA as submitted on 8/22/03 only provided for the 15mg tablet strength. The 5mg and 10mg strengths were added in the 8/14/03 amendment.
File V:/division/dlps/approvrou9.doc
Note: 30 month period expired 1/9/06 for 15mg strength and 2/6/06 for 5mg + 10mg -

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