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November 21, 2005

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: IMPAX Laboratories, Inc.'s Comments Regarding Docket No. 2005P-0352
Bioequivalence Criteria for Generic Versions of Ditropan XL® (oxybutynin
chloride) Extended-Release Tablets

Dear Sir or Madam:

IMPAX Laboratories, Inc. (IMPAX) has reviewed the above-referenced Citizen Petition, submitted on August 29, 2005 by Ortho-McNeil Pharmaceutical, Inc. (the "Petition"), as well as Ortho-McNeil's October 7, 2005 Supplement (the "CP Supplement") to the Citizen Petition. IMPAX also references the September 30, 2005 comments submitted to this docket by Mylan Pharmaceuticals, Inc. (Mylan).

IMPAX also has an interest in this Petition because, like Mylan, IMPAX has submitted an Abbreviated New Drug Application (ANDA) seeking marketing approval for a generic version of Oxybutynin Chloride Extended-Release Tablets. IMPAX conducted all required *in-vivo* bioequivalence studies and demonstrated statistical bioequivalence to the Reference Listed Drug (RLD), Ditropan XL®. Accordingly, IMPAX's ANDA was granted Tentative Approval by the Office of Generic Drugs on February 11, 2005.

IMPAX concurs with the comments submitted by Mylan. Our additional comments contained herein emphasize several key points that refute the position being taken by Ortho-McNeil that ANDA applicants must demonstrate bioequivalence to the RLD based on demonstration of bioequivalence to the R- and S-enantiomers of oxybutynin and the metabolite, desethyloxybutynin. **Appendix 1** of this correspondence presents further arguments from a pharmacokinetic viewpoint based on Ortho-McNeil's own data.

According to publicly available information published by FDA, there are currently three pending ANDAs for generic versions of Oxybutynin Chloride Extended-Release Tablets.¹ These ANDAs have all received Tentative Approval from the Office of Generic Drugs based on, among other things, the demonstration of bioequivalence to a RLD, in this case, Ditropan XL®.

¹ ANDAs 76-745 (IMPAX 5, 10, and 15 mg); 76-702 (Mylan 5 mg); and 76-644 (Mylan 10 mg)

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A tentatively approved ANDA contains data satisfying all of FDA's technical requirements and is eligible for final approval as soon as all relevant patent and exclusivity barriers are overcome².

The patent issue cited in IMPAX's TA letter was with respect to US Patent 6,124,355 and is no longer a barrier to final approval because the US District Court has entered a finding of invalidity with respect to the '355 patent, thus allowing approval of IMPAX's ANDA³. In addition to acceptable bioequivalence data and resolution of all remaining patent barriers to approval, IMPAX's ANDA also contains acceptable labeling and CMC information, thus leading to issuance of tentative approval.

It is IMPAX's position that Ortho-McNeil has engaged the Citizen Petition process merely as a tactic aimed at delaying approval of ANDAs that otherwise qualify for full approval. After reviewing all relevant data, FDA found no significant difference in the R-/S- ratio of the parent or metabolite, even between the extended-release product and immediate-release formulations where input rates ranged nearly 20-fold (Appendix 1). Furthermore, despite Ortho-McNeil's claims of superior safety and efficacy of Ditropan XL over immediate-release products, attributed to the significantly reduced levels of R-desethyloxybutynin isomer (to which they assign the adverse anticholinergic effects), FDA found the results from Ortho-McNeil's clinical studies failed to confirm these claims and thus refused to grant any claim of superiority with respect to safety⁴, suggesting that even significantly different exposures to R-desethyloxybutynin between IR and XL formulations are of minimal clinical significance.

FDA guidelines recommend demonstration of bioequivalence with respect to individual enantiomers only if a drug meets all of the following four criteria:

- (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
- (4) nonlinear 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.

Each of these criteria is further discussed in detail in Appendix 1. However, criterion (4) has clearly not been met in that 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]harmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5 to 20 mg of Ditropan® XL are dose proportional." (emphasis added)

² IMPAX's Tentative Approval letter reads in part:

"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**." (original emphasis)

³ See *Alza Corporation v. Mylan Laboratories et al* (Civil Action No. 1:03CV61), *Alza Corporation v. IMPAX Laboratories* (Civil Action No. C 03-4032 VRW), and 21 U.S.C. § 355(j)(5)(B)(iii)(I)(aa).

⁴ Summary Basis of Approval, Clinical Pharmacology and Biopharmaceutics Review, p. 14.

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.

IMPAX also notes that the clinical data on the R- and S-enantiomers, as cited by Ortho-McNeil, dates back to 1997 and thus were available to FDA prior to its issuance of Tentative Approval letters to IMPAX and Mylan.

The timing of Ortho-McNeil's Citizen Petition is both highly suspect as to its timing and without scientific merit. Accordingly, FDA should take immediate action to deny the Ortho-McNeil petition and grant final approval to IMPAX's ANDA.

Sincerely,
IMPAX Laboratories, Inc.

A handwritten signature in black ink, appearing to read 'Mark C. Shaw', with a stylized flourish at the end.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

APPENDIX 1

**Pharmacokinetic Argument Rebutting Ortho-McNeil's Position
Regarding Demonstration of Bioequivalence Based on the
R- and S- Enantiomers of Oxybutynin**

On August 29, 2005 Ortho-McNeil Pharmaceutical, Inc. (Ortho-McNeil) submitted a Citizen Petition requesting the Food and Drug Administration (FDA) to require that standard BE criteria, C_{max} and AUC, be applied separately to the individual enantiomers of oxybutynin and its active metabolite, desethyloxybutynin, to ensure that approved generic versions of Ditropan XL® Extended-Release Tablets are both bioequivalent and clinically equivalent to the innovator product under both fasting and fed conditions. On October 7, 2005 Ortho-McNeil submitted Supplement 1 to the original Citizen Petition, averring that standard BE criteria be applied to individual enantiomers of oxybutynin and desethyloxybutynin for all generic versions of Ditropan XL Extended-Release Tablets.

According to FDA's guidance document⁵, demonstration of BE with respect to individual enantiomers is needed only if a drug meets all of the following four criteria:

- (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
- (4) nonlinear 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.

It has been demonstrated that the enantiomers of oxybutynin are metabolized to different extents, the enantiomers and their active metabolites exhibit different pharmacodynamic characteristics, and that the primary efficacy and safety activity resides with the minor enantiomer based on *in vitro* data and animal model. Furthermore, Ortho-McNeil's dose proportionality study (Study # C-96-068) indicated that the rate and extent of absorption (AUC and C_{max}) of oxybutynin is linear "dose-wise". Therefore, the focus of the CP was to contend that the absorption of oxybutynin is nonlinear and is dependent on the input rate, but not the dose. However, the rationales and the data presented in the CP and Supplement to the CP are inconsistent with pharmacokinetic principles and regulatory guidelines as presented below:

1. Ortho-McNeil's data (Study #C-96-068) showed that when the input rate increased 2-fold, from 2 x 5 mg or 1 x 10 mg to 4 x 5 mg of Ditropan XL, the metabolite/parent drug (M/P) ratios remained constant for both R- and S- isomers. In addition, the R/S ratios also remained constant for both oxybutynin and desethyloxybutynin, indicating that the absorption of oxybutynin, with respect to the individual isomers, is in fact linear even when "input rates" varied by 2-fold.

Although some statistically significant differences were observed between Ditropan XL products with 2-fold differences in input rates in M/P ratios for R- and S- isomers (Table 2 of Supplement 1 to Docket No 2005P-0352) and in R/S ratios for parent and metabolite (Table 4 of Supplement 1 to Docket No 2005P-0352), the differences were small, ranging from 0% to 12.5% across all pair-wise comparisons (Table 1). Furthermore, these differences in ratios generally are significantly smaller than the variation (expressed as %CV) associated with the R/S ratios or M/P ratios observed for the individual products (Table 1).

⁵ Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March 2003.

Based on the results of Study C-96-068, we conclude that the extent and rate of absorption of racemic and enantiomeric oxybutynin clearly are linear for input rates that differ by 2-fold:

2. Even when comparing two "non-bioequivalent" formulations (IR vs. XL) that are designed to have up to 20-fold differences in input rates (see Table 2), with a pharmacokinetic consequence of substantially different oxybutynin and desethyloxybutynin levels and M/P ratios (Table 1 of Docket No. 2005P-0352), the differences in R/S ratios across IR and Ditropan XL® are small, only approximately 20% for both parent and metabolite (see Table 3 of Docket No. 2005P-0352).

Table 2 shows the estimated *in vivo* input rates for R-isomer for IR and XL formulations, calculated as described below, and the R/S ratios for AUC and C_{max} for oxybutynin and desethyloxybutynin as reported in Tables 3 and 4 in Ortho-McNeil's Citizen's Petition, Docket No. 2005P-0352, Supplement 1. The *in vivo* input rates for R-isomer of IR and Ditropan XL were estimated assuming the absorption is completed by the time of t_{max} . The input rates for R-oxybutynin for 5 mg IR and for Ditropan XL 10 mg were estimated based on Figure 1 and Table 1 of the Ditropan XL package insert. Since pharmacokinetics are linear for oxybutynin IR and Ditropan XL, the input rates for other strengths of oxybutynin IR and Ditropan XL were estimated assuming the rates are directly proportional to dose within each formulation category. As depicted in Figure 1, the R/S ratios for oxybutynin and desethyloxybutynin differed by about 20% when input rates for R-oxybutynin increased almost 20-fold from approximately 0.39 mg/hr (Ditropan XL, 5 mg) to approximately 7.5 mg/hr (IR) (Figure 1). It should be noted that the input rate of R-oxybutynin is approximately $\frac{1}{2}$ of total oxybutynin input rate; therefore, similar relationships between input rate and R/S ratios are expected for S-oxybutynin.

The above analyses clearly indicate that the differences between generic formulations and Ditropan XL will be sensitively detected by comparing AUC and C_{max} values of oxybutynin and desethyloxybutynin, and there is no need to further compare AUC and C_{max} values of the R- and S-isomers.

3. Even in the presence of significantly different input rates and substantially different pharmacokinetic profiles between IR and Ditropan XL, FDA's 1998 review of Ditropan XL concluded that "According to the medical officer, Dr. Dan Shames (HFD-580), and the statistician, Sonia Castillo (HFD-715), the results of the clinical studies do not support a superiority claim (Ditropan XL over Ditropan IR). Therefore, although the PK-PD simulations show a trend for decreased side effects (dry mouth) for Ditropan XL relative to oxybutynin IR, results of the clinical studies failed to confirm these results in a clinically significant manner." (see SBA, Section 7, PK/PD Relationship and Population Pharmacokinetics) The lack of clear differences in side effect profiles in clinical studies between IR and XL formulations indicates that the change in the exposures to R-desethyloxybutynin in the XL formulation relative to the IR formulation are of minimal clinical significance.

In its October 7, 2005 supplement to the original Citizen's Petition, Ortho-McNeil pointed out that "at the time of the review in 1998, the recent analysis of R- to S- concentration ratios were not available, even for the studies cited in the SBA".

This was in response to comments submitted by Mylan Pharmaceuticals, Inc., who cited an FDA reviewer's comment that "the R/S ratio of oxybutynin and desethyloxybutynin is not significantly different between Ditropan XL and oxybutynin IR". We are confident in FDA's comment that "the R/S ratio of oxybutynin and desethyloxybutynin is not significantly different between Ditropan XL® and oxybutynin IR" was based on FDA's own analysis of the R- and S- data presented in the NDA submission. As presented above, our analysis of Ortho-McNeil's data agree with FDA's assessment that even with a large difference in the input rates, the enantiomer concentration ratios are not significantly different between IR and Ditropan XL.

In conclusion, IMPAX disagrees with Ortho-McNeil's contention that oxybutynin exhibits nonlinear absorption in which the enantiomer concentration ratio changes with the drug input rate. Analysis of the data provided by Ortho-McNeil clearly indicates that the extent and rate of absorption of oxybutynin racemates and enantiomers of Ditropan XL is linear and the R/S ratios are constant across input rates that differed by 2-fold.

It can be conservatively concluded that the R/S ratios between bioequivalent generic versions of Ditropan XL and Ditropan XL would be the same for both oxybutynin and desethyloxybutynin. Furthermore, 2-fold differences in M/P ratios and 20% differences in R/S ratio between IR and Ditropan XL did not result in clinically significant differences in side effects. These data strongly support that there is no scientific need for requiring demonstration of BE for individual enantiomers of either oxybutynin or desethyloxybutynin.

Table 1. The R/S Ratios for Oxybutynin and Desethyloxybutynin and Metabolite/Parent Ratios for R- and S-Isomers After Dosing with 2 x 5 mg, 1 x 10 mg, or 4 X 5 mg Ditropan XL® (Alza Study C-96-068)

Daily Dose	PK Parameter	Mean R-to-S Ratio		Mean Metabolite-to-Parent Ratio	
		R-Oxy/S-Oxy-	R-Des/S-Des.	R-Des/R-Oxy.	S-Des/S-Oxy.
A. 2x5 mg	AUCinf	0.58	1.69	8.58	3.02
B: 1x10 mg	AUCinf	0.56	1.68	8.59	2.89
C :4x5 mg	AUCinf	0.58	1.65	8.78	3.25
SD					
A. 2x5 mg	AUCinf	0.12	0.5	1.79	0.78
B: 1x10 mg	AUCinf	0.09	0.56	2.65	0.54
C :4x5 mg	AUCinf	0.14	0.57	1.97	0.9
%CV ¹					
A. 2x5 mg	AUCinf	20.7	29.6	20.9	25.8
B: 1x10 mg	AUCinf	16.1	33.3	30.8	18.7
C :4x5 mg	AUCinf	24.1	34.5	22.4	27.7
% Diff. ²					
A-B	AUCinf	3.6	0.6	-0.1	4.5
C-B	AUCinf	3.6	-1.8	2.2	12.5
C-A	AUCinf	0.0	-2.4	2.3	7.6
SD					
A. 2x5 mg	Cmax	0.12	0.42	3.67	0.96
B: 1x10 mg	Cmax	0.11	0.42	3.86	0.92
C :4x5 mg	Cmax	0.11	0.46	3.15	0.95
%CV					
A. 2x5 mg	Cmax	21.4	21.9	32.7	28.7
B: 1x10 mg	Cmax	20.0	21.8	34.5	28.1
C :4x5 mg	Cmax	18.3	24.0	28.2	26.4
% Diff.					
A-B	Cmax	1.8	-0.5	0.3	2.1
C-B	Cmax	9.1	-0.5	-0.1	10.1
C-A	Cmax	7.1	0.0	-0.4	7.8

The values for the mean and standard deviation (SD) were obtained from Tables 2 and 4 of Docket No.2005P-0352: Supplement to Citizen Petition.

¹The values of %CV were taken directly from Tables 2 and 4 when available. Otherwise, they were calculated as SD/mean*100.

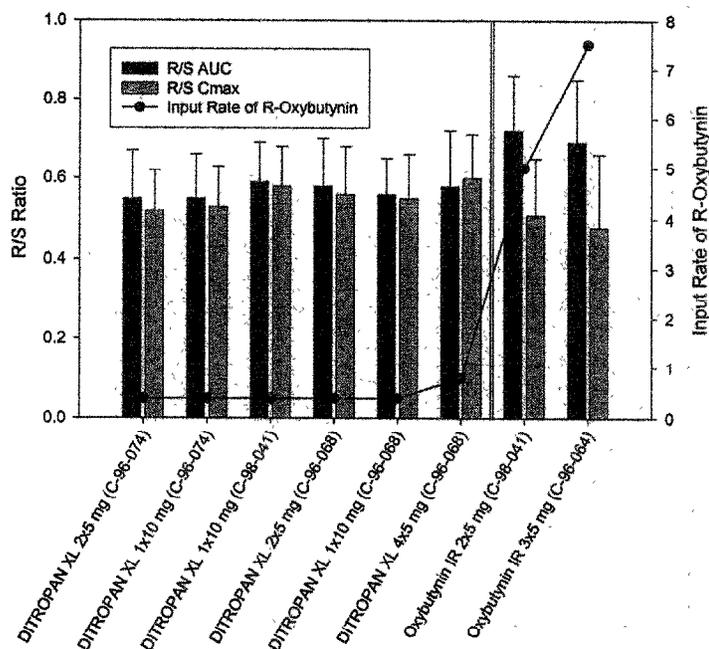
²%Diff is the percent difference between mean values of either A vs B, C vs B or C vs A.

Table 2: Estimated *In Vivo* Input Rate of R-Oxybutynin and Reported R/S Ratios for Oxybutynin and Desethyloxybutynin Determined for Various IR and ER Regimens of Oxybutynin

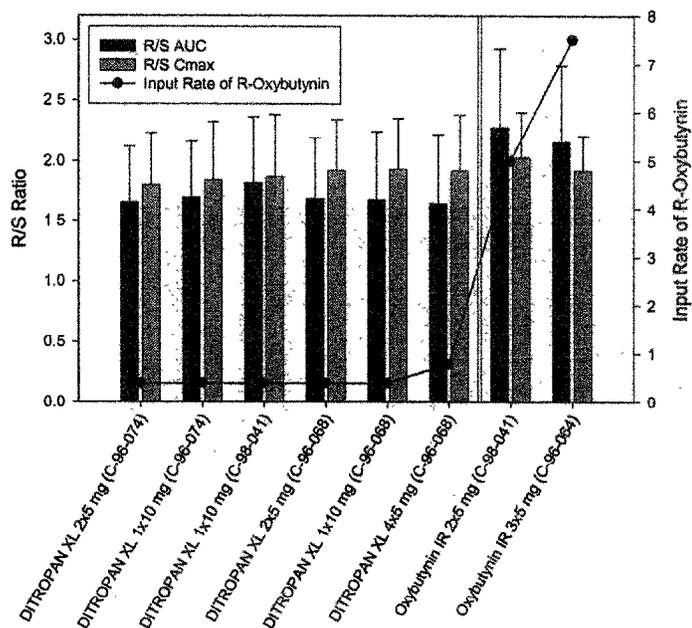
Regimen	Input rate of R-oxybutynin (mg/hr) ^a	ALZA Study No	R/S Ratios AUC (SD)	R/S Ratios C _{max} (SD)
Oxybutynin				
DITROPAN XL 2x5 mg	0.39	C-96-074	0.55 (0.12)	0.52 (0.10)
DITROPAN XL 1x10 mg	0.39	C-96-074	0.55 (0.11)	0.53 (0.10)
DITROPAN XL 1x10 mg	0.39	C-98-041	0.59 (0.10)	0.58 (0.10)
DITROPAN XL 2x5 mg	0.39	C-96-068	0.58 (0.12)	0.56 (0.12)
DITROPAN XL 1x10 mg	0.39	C-96-068	0.56 (0.09)	0.55 (0.11)
DITROPAN XL 4x5 mg	0.79	C-96-068	0.58 (0.14)	0.60 (0.11)
Oxybutynin IR 5 mg	2.50	Not available	Not available	Not available
Oxybutynin IR 2x5 mg	5.00	C-98-041	0.72 (0.14)	0.51 (0.14)
Oxybutynin IR 3x5 mg	7.50	C-96-064	0.69 (0.16)	0.48 (0.18)
Desethyloxybutynin				
DITROPAN XL 2x5 mg	0.39	C-96-074	1.66 (0.46)	1.80 (0.43)
DITROPAN XL 1x10 mg	0.39	C-96-074	1.70 (0.46)	1.84 (0.48)
DITROPAN XL 1x10 mg	0.39	C-98-041	1.82 (0.54)	1.87 (0.51)
DITROPAN XL 2x5 mg	0.39	C-96-068	1.69 (0.50)	1.92 (0.42)
DITROPAN XL 1x10 mg	0.39	C-96-068	1.68 (0.56)	1.93 (0.42)
DITROPAN XL 4x5 mg	0.79	C-96-068	1.65 (0.57)	1.92 (0.46)
Oxybutynin IR 5 mg	2.50	Not available	Not available	Not available
Oxybutynin IR 2x5 mg	5.00	C-98-041	2.28 (0.65)	2.03 (0.37)
Oxybutynin IR 3x5 mg	7.50	C-96-064	2.16 (0.63)	1.92 (0.29)

^a *In vivo* input rates of R-oxybutynin following a single dose of DITROPAN XL® 10 mg and oxybutynin IR 5 mg were estimated by dividing the total dose of R-oxybutynin (=1/2 of the total dose) by the t_{max}, assuming 100% absorption of R-oxybutynin was completed by t_{max}. The t_{max} of R-oxybutynin of DITROPAN XL 10 mg (12.7 hours) was obtained directly from Table 1 and the t_{max} of R-oxybutynin (1 hour) of oxybutynin IR 5 mg was estimated from Figure 1. *In vivo* input rates of R-oxybutynin of DITROPAN XL 20 mg and oxybutynin IR 10 and 15 mg were estimated to be directly proportional to DITROPAN XL 10 mg and oxybutynin 5 mg, respectively.

Figure 1: Estimated *In Vivo* Input Rates (mg/hr) and Reported R/S ratios[†] for Oxybutynin and Desethyloxybutynin of (A) oxybutynin and (B) desethyloxybutynin After Various Doses of Oxybutynin IR and Ditropan XL®
(A) Oxybutynin



(B) Desethyloxybutynin



[†]R/S ratios were obtained from Tables 3 and 4 of Study #C-96-074, #C-98-041, and #C-96-088 (Ortho-McNeil Citizen Petition Supplement 1; Docket No. 2005P-0352)