

MYLAN PHARMACEUTICALS INC

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September 30, 2005 00072005 OCT -3 P1 :54

VIA FEDERAL EXPRESS

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

**RE: Comments of Mylan Pharmaceuticals Inc. on Docket No. 2005P-0352 :
Bioequivalence Criteria for Generic Versions of Ditropan XL®
(oxybutynin chloride) Extended-Release Tablets**

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. ("Mylan") submits these comments in response to the above-referenced citizen petition filed by Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil" or "Petitioner") on August 29, 2005 (the "Petition").

Mylan has an interest in the Petition, because Mylan has submitted abbreviated new drug applications ("ANDAs") for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg, and the Petitioner has requested the Food and Drug Administration ("FDA" or "Agency") to require the application of bioequivalence criteria separately to oxybutynin and its active metabolite, desethyloxybutynin in both fasting and food effect studies, ostensibly to ensure that approved generics are therapeutically equivalent to the innovator product.

I. INTRODUCTION

Based on the data submitted in Mylan's ANDAs regarding the parent drug and active metabolite, FDA tentatively approved Mylan's ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg on January 12, 2005. The Petition provides no new information, which would require Mylan to conduct any additional bioequivalence testing prior to receiving final approval¹. Accordingly, Mylan believes that the Petition is without merit as far as it applies to the approval of Mylan's ANDAs, which have already received tentative approval.

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¹ Ortho-McNeil does not provide any new information, which they did not know of at the time of filing of Mylan's ANDAs. The Petition appears to be nothing more than an attempt to manipulate the citizen petition process to delay generic competition as on September 27, 2005, the United States District Court for the Northern District of West Virginia held that Mylan does not infringe Alza Corporation's patent and that the patent is invalid, thus terminating Mylan's 30-month stays.

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II. THE CITIZEN PETITION DOES NOT DEMONSTRATE ANY NECESSITY TO MODIFY THE LONGSTANDING REQUIREMENTS AND STANDARDS FOR DEMONSTRATING BIOEQUIVALENCE TO DITROPAN XL.

A. Ortho-McNeil interprets FDA guidance on bioavailability and bioequivalence to require the measurement of desethyloxybutynin as a prerequisite for approval.

At the time Mylan submitted its ANDAs, FDA Guidance recommended measuring an active metabolite if it is formed as a result of gut wall or other presystemic metabolism and contributes meaningfully to safety and/or efficacy. FDA Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (October 2000) (hereinafter, “FDA Guidance”)². The Petitioner alleges that oxybutynin’s major metabolite, desethyloxybutynin, is formed as a result of presystemic gut-wall metabolism and that this metabolite contributes meaningfully to the safety and efficacy profile, so it should be considered in assessing bioequivalency.

Mylan agrees with Ortho-McNeil that oxybutynin’s major metabolite, desethyloxybutynin, is formed as a result of gut wall or other presystemic metabolism, and that it contributes meaningfully to safety and/or efficacy.

Accordingly, in its pivotal bioequivalence studies, Mylan measured both the parent and active metabolite under fasting and fed conditions. Mylan conducted its food studies according to the established FDA guidance at the time of the submission of Mylan’s ANDAs. *See* Guidance for Oral Extended (Controlled) Release Dosage Form In Vivo Bioequivalency and In Vitro Dissolution Testing (September 1993); *see also* FDA Guidance. FDA Guidance, however, clearly states that because the parent drug is more sensitive to changes in formulation performance than a metabolite, the data from the measurement of an active metabolite can be used as supportive evidence of equivalency. *Id.* Based on the review of the data contained in Mylan’s applications, FDA tentatively approved Mylan’s ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg on January 12, 2005.

The Petitioner has failed to provide any new information which was not known to the Agency at the time Mylan’s ANDAs were given tentative approval. As a result, regardless of when and how the Agency ultimately decides the merits of the Petition, the approval of Mylan’s ANDAs should not be delayed.

² In March 2003, the Agency revised the FDA Guidance, however, the requirements and value for the measurement of an active metabolite did not change

III. ORTHO-MCNEIL FAILS TO PROVIDE ADEQUATE RATIONALE TO MEASURE INDIVIDUAL ENANTIOMERS IN BE STUDIES.

A. **Ortho-McNeil suggests that the Agency should require generic applicants to measure R- and S- enantiomers of both oxybutynin and desethyloxybutynin.**

In addition to measuring oxybutynin and its major metabolite, desethyloxybutynin, the Petitioner requests the Agency to require generic applicants to measure R- and S-enantiomers of both the parent and active metabolite. This request is simply unfounded and contrary to FDA's well-established guidance.

FDA Guidance for BE studies recommends measurement of the racemate using an achiral assay. "Measurement of individual enantiomers in BE studies is recommended only when all of the following conditions are met: (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 (as expressed by a change in the enantiomer concentration ratio with change in input rate of the drug) for at least one of the enantiomers. In such cases, FDA recommends that BE factors be applied to the enantiomers separately." FDA Guidance (emphasis added)³.

The Petition fails to provide any support that the fourth factor, nonlinear absorption, is present. In fact, the Pharmacokinetics section of Ditropan XL's Final Printed Labeling (FPL) (Revised June 2004), clearly 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). Because the PK parameters are "dose proportional", there is no reason to believe that nonlinear absorption occurs.

In addition, based on the literature cited, Mylan concurs with the FDA reviewer of Ditropan XL who noted that the "R/S ratio of oxybutynin and desethyloxybutynin were not significantly different between Ditropan XL and oxybutynin IR." Summary Basis of Approval (SBOA) of the Clinical Pharmacology and Biopharmaceutics Review, p. 14. Therefore, the ER formulation does not bestow any unique properties to the relative proportions of R-to-S for parent or metabolite. Despite the different rates of input and delivery to the gastrointestinal tract for ER vs. IR formulations, the relative ratios of exposure for R-to-S do not change. Thus, provided that two extended-release formulations have been found to be bioequivalent for both the parent and metabolite by an achiral method, ratios of R-to-S enantiomers should be equivalent for parent and metabolite.

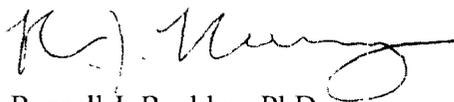
³ Consistent with the requirements for the measurement of the parent drug and active metabolite, in March 2003, when the Agency revised the FDA Guidance, the requirements for the separate measurement of the enantiomers did not change.

Accordingly, the Petitioner does not meet the criteria for requiring the separate measurement of enantiomers. Mylan has conducted satisfactory studies with regard to developing a formulation bioequivalent to Ditropan XL as evidenced by FDA's granting of tentative approval on January 12, 2005.

IV. CONCLUSION

Given these facts, and regardless of the ultimate outcome of the Petition, there is no reason that the Petition should delay approval of Mylan's already tentatively approved ANDAs.

Respectfully submitted,



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cc: Elizabeth Dickinson, *Office of Chief Counsel (via e-mail)*
Gary Buehler, *Office of Generic Drugs (via e-mail)*