DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 9 2006

Minnie Baylor-Henry
Vice-President, Medical and Regulatory Affairs
Ortho-McNeil Pharmaceutical, Inc.
Camp Hill Road
Ft. Washington, PA 19034

Docket No. 2005P-0352/CP1 & SUP1

Dear Ms. Baylor-Henry:

This letter responds to your citizen petition dated August 29, 2005 (Petition), and corresponding supplement dated October 7, 2005 (Supplement).[1] You ask the Food and Drug Administration (FDA) to require that standard bioequivalence criteria be applied separately to oxybutynin and its active metabolite, desethyloxybutynin, to ensure that approved generic versions of Ditropan XL (oxybutynin chloride) are both bioequivalent and clinically equivalent to the innovator product. You also request that FDA apply bioequivalence criteria to the R- and S-enantiomers of oxybutynin and desethyloxybutynin. Finally, you request that all bioequivalence studies be conducted under both fasting and fed conditions. For the reasons described below, your petition is granted in part and denied in part.

I. BACKGROUND

A. Ditropan XL

Oxybutynin has been marketed in the United States as Ditropan for more than 25 years as an immediate release (IR) tablet. Ditropan XL (new drug application (NDA) 20-897) is an extended release (ER) prescription drug product marketed by Ortho-McNeil Pharmaceuticals, Inc. Ditropan XL is indicated for, among other things, the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, chronic conditions that affect approximately 33 million people in the United States. As described in your petition, overactive bladder symptoms increase with

[1] We have also reviewed all comments filed in Docket No. 2005P-0352.

2005P-0352 PAV 1

age and affect an increasingly large number of elderly adults. Ditropan XL reduces an incontinent patient's urge to urinate as frequently by acting as an anticholinergic[2] agent and a smooth muscle relaxant. The NDA for Ditropan XL is sponsored by the ALZA Corporation (ALZA) and received FDA approval in 1998.[3] FDA designated Ditropan XL as the reference listed drug (RLD) for oxybutynin ER.

B. Statutory and Regulatory Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act)(21 U.S.C. 355(j)), which establishes the current approval process for abbreviated new drug applications (ANDAs). The ANDA approval process is different from and generally less onerous than the NDA approval process for new drug products. An NDA must demonstrate that the drug product for which the applicant requests approval is safe and effective when used according to labeling. By contrast, an ANDA relies fundamentally on FDA's previous finding that the listed drug to which the ANDA refers is safe and effective.

To rely on this finding, an ANDA applicant must demonstrate, among other things, that its generic[4] drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act). Section 505(j)(8)(B)(i) of the Act states that a generic drug product is bioequivalent to the RLD if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .[5]

In 21 CFR 320.1(e), FDA defines bioequivalence (in part) as

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when

---

[2] *Anticholinergics* are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. The nerve fibers of the parasympathetic system are responsible for the involuntary movements of smooth muscles present in the gastrointestinal tract, urinary tract, lungs, etc. Anticholinergics are divided into three categories in accordance with their specific targets in the central and/or peripheral nervous system: antimuscarinic agents, ganglionic blockers, and neuromuscular blockers (see definition of anticholinergics in Health & Medicine enotes.com at http://health.enotes.com).

[3] ALZA and Ortho-McNeil Pharmaceuticals, Inc. are both Johnson & Johnson companies.

[4] For purposes of this response, the term *generic* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[5] See also 21 CFR 320.1(e), 320.23(b).

> administered at the same molar dose under similar conditions in an appropriately designed study.

The scientific premise underlying the Hatch-Waxman Amendments is that drug products that are both bioequivalent and pharmaceutically equivalent[6] are therapeutically equivalent, meaning that the drugs generally may be substituted for each other.[7] FDA regulations at 21 CFR part 320 establish acceptable methodologies for determining the bioequivalence of drug products. FDA regulations in 21 CFR 320.24 list the in vivo and in vitro methods of determining bioavailability or bioequivalence for a drug product, in descending order of accuracy, sensitivity, and reproducibility. These tests include studies such as pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies.

Section 320.24(b)(1)(i) provides that the most accurate method for testing the bioavailability or bioequivalence of a drug product is:

> An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time.

The regulation continues, "This approach is particularly applicable to dosage forms intended to deliver the active moiety to the blood stream for systemic distribution within the body." Given that oxybutynin and its active metabolite, desethyloxybutynin, can be readily measured in plasma, this approach is applicable to ANDA applicants seeking approval of generic ER oxybutynin products. The choice of which study design to use is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug. The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements. *See, e.g., Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

---

[6] Pharmaceutically equivalent drug products have identical dosage forms and contain identical amounts of the identical active ingredient, and meet the identical compendial or other applicable standard of identity, strength, quality, and purity. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling. See 21 CFR 320.1; FDA's *Approved Products with Therapeutic Equivalence Evaluations* (Orange Book), p. vii.

[7] A generic drug that establishes bioequivalence as well as pharmaceutical equivalence is coded A as therapeutically equivalent to the RLD in the Orange Book. Drug products that the Agency does not currently consider therapeutically equivalent to other pharmaceutically equivalent products are coded B.

II. DISCUSSION

A. Apply Bioequivalence Criteria to Oxybutynin and Its Active Metabolite Desethyloxybutynin

You ask FDA to require that generic versions of Ditropan XL show bioequivalence for both oxybutynin and the active metabolite desethyloxybutynin. In March 2003, FDA issued a guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE Guidance).[8] The BA/BE Guidance provides recommendations concerning the measurement of either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolite(s) in the determination of the drug's bioavailability and bioequivalence (pp. 17-18). For bioequivalence studies, the BA/BE Guidance generally recommends measurement of only the ***parent*** drug (the moiety released from the dosage form), rather than the metabolite (p. 18). The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination" (BA/BE Guidance, p. 18).

The BA/BE Guidance describes two situations when the above general recommendation (i.e., measuring the parent drug only) does not apply. The first situation is when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The second situation is when a metabolite may be formed as a result of gut wall or other presystemic metabolism and the metabolite contributes meaningfully to safety and/or efficacy. With respect to the second situation, the BA/BE Guidance (p. 18) explains:

> If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

The first situation does not apply in the case of Ditropan XL. The plasma concentrations of oxybutynin, the parent drug, can be determined with accuracy and reproducibility. This is not a case where oxybutynin concentrations are too low to allow reliable analytical measurement for an adequate length of time.

The second situation, however, does apply to oxybutynin. We conclude that based on the available scientific evidence, desethyloxybutynin is formed as a result of gut wall or other presystemic metabolism, and it contributes meaningfully to the safety and/or efficacy of

[8] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

the drug product.[9] Consequently, we recommend that metabolite data for desethyloxybutynin be measured and that the data be used to provide supportive evidence of therapeutic outcome.

You propose, however, that FDA apply what you refer to as the standard bioequivalence criteria to the metabolite, in addition to the parent drug, for all ANDAs that refer to Ditropan XL as the listed drug[10] (Petition at 1, 3-4). You assert that the drug input rate differs among ER oxybutynin products, citing comparisons of Ditropan XL to Cystrin CR, which is an oxybutynin ER drug marketed in Finland (Petition at 10, 19-22). You argue that the ratio of metabolite to parent concentration is important because the metabolite has a greater effect on the salivary gland and, thus, may increase unpleasant side effects. You claim that this effect ultimately affects safety and efficacy. Therefore, you state that bioequivalence criteria applied to the metabolite will ensure the same safety and efficacy profile as Ditropan XL.

The Agency disagrees with your suggestions that we should apply what you refer to as "bioequivalence criteria" to both oxybutynin (the parent) and desethyloxybutynin (the metabolite). As explained above, the concentration-time profile of the parent drug is more sensitive to changes in formulation performance when compared with that of a metabolite, which is more reflective of metabolite formation, distribution, and elimination. We do not expect ANDA applicants for oxybutynin chloride ER tablets to apply bioequivalence statistical criteria to the metabolite to demonstrate bioequivalence. Although we consider the data for the metabolite as supportive evidence of bioequivalence, we believe that it is unnecessary and inappropriate to require generic applicants to apply bioequivalence statistical criteria to the active metabolite to demonstrate bioequivalence. This approach is consistent with that set forth in the BA/BE Guidance, which, as you also acknowledge, explains that metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

You present no persuasive evidence to demonstrate that a generic oxybutynin ER drug product, approved in accordance with this recommendation in the BA/BE Guidance as well as other applicable statutory and regulatory requirements, would present a problem regarding therapeutic equivalence to the RLD. Therefore, your petition is granted to the extent that we expect ANDA applicants to measure levels of the metabolite

---

[9] Because both you and Mylan agree with this conclusion, we do not include in this response further explanation on this point.

[10] You also assert that reliance on the average bioequivalence levels of oxybutynin alone without assessment of desethyloxybutynin may result in inappropriate bioequivalence determinations for this type of ER product, suggestive of a potential bioequivalence problem that warrants assessment under 21 CFR 320.33(f) (Supplement at 1). Section 320.33 enumerates criteria to be used in evaluating whether products previously believed to be pharmaceutical equivalents and pharmaceutical alternatives present actual or potential bioequivalence problems. As articulated above, we expect to only approve generic versions of Ditropan XL that are bioequivalent to Ditropan XL. We have no reason to expect potential or actual bioequivalence problems for generic versions of Ditropan XL that meet applicable statutory and regulatory requirements as well as the recommendations set forth above.

desethyloxybutynin that can be used to provide supportive evidence of comparable therapeutic outcome, but denied with respect to your request to apply what you refer to as standard bioequivalence criteria to the metabolite.

B. Apply Bioequivalence Criteria to Data from Both Fasting and Fed Studies of Oxybutynin and Desethyloxybutynin

You request that bioequivalence criteria be applied to the data from studies of both oxybutynin and desethyloxybutynin conducted under both fasting and fed conditions. You indicate that you conducted a pharmacokinetic study in normal subjects to investigate the effect of food on the absorption of the parent drug and the active metabolite, desethyloxybutynin. You state that the study shows that food affected the parent drug and the active metabolite differently (Petition at 15).

FDA's guidance on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (Food Effect Guidance),[11] issued in December 2002, states that fed bioequivalence studies are conducted for ANDAs to demonstrate their bioequivalence to the RLD under fed conditions. For all orally administered modified-release drug products such as oxybutynin ER, the Agency indicates that food effects are most likely to result from a complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance (Food Effect Guidance, p. 4).

In the Food-Effect Guidance, FDA recommends that food-effect bioavailability and fed bioequivalence studies be performed for all modified-release dosage forms of drugs (p. 4).[12] Consequently, FDA expects all ANDA applicants for oxybutynin ER products to measure the parent drug, oxybutynin, and the active metabolite, desethyloxybutynin, to demonstrate bioequivalence in both fasting and fed states. The Agency expects the studies to demonstrate that the generic oxybutynin ER product exhibits equivalent in vivo performance to Ditropan XL in the presence or absence of food. Because we expect generic oxybutynin ER applicants to measure oxybutynin and desethyloxybutynin in both fasting and fed studies, your request is granted in part. However, as explained in section II.A, although we expect the desethyloxybutynin metabolite to be measured and the metabolite data to be used to provide supportive evidence of comparable therapeutic outcome. We do not expect bioequivalence statistical criteria to be applied to the metabolite data.

---

[11] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[12] For ANDA applicants, the Food Effect Guidance recommends that fasting and fed bioequivalence studies be conducted for all orally administered modified-release drug products (p. 4).

C. Apply Bioequivalence Criteria Separately to the R- and S-Enantiomers of Both Oxybutynin and Desethyloxybutynin

In addition to proposing that bioequivalence criteria be applied separately to the parent drug and the metabolite, you propose that BE criteria be applied in a food effect study to all four enantiomers of oxybutynin (parent) and desethyloxybutynin (metabolite) , which are: (1) R-oxybutynin, (2) S-oxybutynin, (3) R-desethyloxybutynin, and (4) S-desethyloxybutynin. You maintain that for certain chiral drugs, such as oxybutynin, the R-to-S concentration ratios of the parent and metabolite change with drug input rate. You indicate that the drug input rate is a function of the delivery system, release rate, rate of gut wall metabolism, absorption, and gastrointestinal transit time, apparently suggesting that all four enantiomers of the active ingredient and the active metabolite must be measured and criteria applied to establish bioequivalence (Petition at 2).

Enantiomers[13] are mirror image molecules that cannot be superimposed on each other. Enantiomers exhibit optical activity, and each enantiomer of a pair is capable of rotating plane polarized light the same number of degrees in opposite directions. Other physical properties of the enantiomers are the same. In addition, enantiomers exhibit configuration around a stereocenter carbon wherein one enantiomer will be configured right handedly (R) and the other will be configured left handedly (S).

FDA's BA/BE Guidance states that the measurement of individual enantiomers in bioequivalence studies is recommended only when ***all*** of the following four conditions are met (p. 19):

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 the input rate of the drug) for at least one of the enantiomers.

Relatively few drugs will meet the four conditions that call for measurement of individual enantiomers to determine bioequivalence. As discussed below, Ditropan XL does not meet two of the four conditions.

1. Enantiomers Exhibit Different Pharmacodynamic and Pharmacokinetic Characteristics

[13] Also referred to as stereoisomers or isomers.

With respect to the first two conditions described in the BA/BE Guidance, relevant scientific evidence supports the conclusion that Ditropan XL meets these conditions; the enantiomers exhibit different pharmacodynamic and pharmacokinetic characteristics.[14]

2. *Primary Efficacy and Safety Activity Does Not Reside with the Minor Enantiomer*

In the petition, you maintain that R-oxybutynin is the minor enantiomer as defined by total and maximum systemic exposure (AUC_{INF} and C_{MAX}) compared to S-oxybutynin, whereas R-desethyloxybutynin is the major enantiomer of the active metabolite pair when compared to S–desethyloxybutynin (Petition at 18).

You state that for oral dosage forms, there is stereoselective metabolism[15] of racemic oxybutynin, oxybutynin that contains both left- and right-handed enantiomers. You state that the effect of this stereoselection is to decrease the bioavailability of R-oxybutynin such that its concentrations (C_{MAX} and AUC_{INF}) are less than those for S-oxybutynin (Petition at 18). Studies submitted by ALZA in support of the original NDA for Ditropan XL[16] support your argument that R-oxybutynin when compared with S-oxybutynin has a lower plasma concentration and is the minor enantiomer.

You state that R-oxybutynin (i.e., the minor enantiomer) compared with S-oxybutynin is primarily responsible for the anticholinergic effects of oxybutynin that contribute to both clinical efficacy and safety of the drug (Petition at 18).

You rely on the following studies to support your contention that the primary efficacy and safety activity resides with the R-enantiomer of oxybutynin. First, you cite an animal study (with both in vitro and in vivo components) conducted by Noronha-Blob et al.[17] in

---

[14] Because you agree with this conclusion, we do not include in this response further explanation on this point.

[15] *Stereoselective* means relating to or being a reaction or process producing a stereoisomer having one particular configuration regardless of the stereoisomeric configuration of the reactant (defined in *Merriam-Webster Online* at http://www.merriam-webster.com).

[16] The Alza Corporation submitted the following pharmacokinetic and bioavailability studies in support of NDA 20-897:

1. C-96-010, which evaluated the pharmacokinetics and safety of oxybutynin following administration of Ditropan XL, 3 x 5 mg every day for 4 days, compared with 5-mg Ditropan (Immediate Release) administered every 8 hours for 4 days.
2. C-96-068, which evaluated dose proportionality of Ditropan XL.
3. C-96-074, which evaluated the effect of food on the pharmacokinetics and bioavailability of Ditropan XL relative to Ditropan.
4. C-97-015, which evaluated the bioequivalence of clinical and commercial batches of Ditropan XL.

[17] Noronha-Blob L, Kachur JF. Enantiomers of oxybutynin: *in vitro* pharmacological characterization at M1, M2, and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis, and salivary secretion in guinea pigs. *J Pharmacol Exp Ther,* 1991; 256:562-567.

which the authors report that oxybutynin's antimuscarinic activity[18] is stereoselective in animal tissues. The in vitro portion of this study, performed in 1991, purportedly demonstrates higher anticholinergic activity in the R-enantiomer of oxybutynin than the S-enantiomer in animal tissues. This study, however, does not offer persuasive evidence to demonstrate that the primary pharmacological activity (safety/efficacy) of the drug resides with the minor enantiomer, R-oxybutynin, of Ditropan XL. Because the relevant portion of the Noronha-Blob study was an in vitro study performed in animal tissue, the results do not provide persuasive support for your assertion that the primary safety and efficacy of the drug reside with the R-enantiomer of oxybutynin when administered to humans. Currently, there is no validated model to demonstrate that an animal study (with in vitro and in vivo components) can reasonably predict the relative contribution of the enantiomers to the safety and effectiveness of oxybutynin in humans. In vitro drug testing and pre-clinical results are not always predictive of the drug's performance in humans. Factors such as protein binding, tissue distribution, and the ability of the drug to reach the site of action can all impact the clinical effects of the drug or metabolite once inside the human body. These factors are difficult to account for in pre-clinical and/or in vitro studies, in the absence of a well-validated model. Therefore, the correlation of such in vitro studies to clinical results is not reliable without specific clinical testing.

The best way to determine the effect of R-oxybutynin in humans would be to administer the enantiomer to human subjects in a well-controlled clinical trial. You have not provided such a study to support your argument. 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.

Also, the authors of the Noronha-Blob study expressed doubts regarding any pharmacological advantages offered by the R-oxybutynin enantiomer, as stated below:

> Collectively, the data suggest that the activity of (R/S) OXY resides predominantly in the (R)-enantiomer. However, it appears that (R) OXY may offer no significant pharmacological advantage over (R/S) OXY in terms of its principal therapeutic and side effect profile.

You observe the following based on two additional studies:

---

[18] *Antimuscarinic receptors* are agents that block or counteract the *muscarinic receptors*, which are *cholinergic receptors* that are stimulated by the alkaloid *muscarine* and blocked by *atropine*; they are found on autonomic effector cells and on central neurons in the thalamus and cerebral cortex. Three types may be distinguished on the basis of pharmacologic specificity and five types on the basis of molecular structure; a number of differing nomenclatures have been applied to these types (see the definition of *muscarinic receptor*, under *receptor*, in *Dorland's Medical Dictionary* at http://www.merckmedicus.com).

- You state that R-oxybutynin also was reported to be more potent than S–oxybutynin in a study by Kachur et al. that used in vitro and in vivo assays related to the safety and efficacy of oxybutynin.[19]

- You state that a study by Sathyan, Hu, et al. shows that the minor enantiomer contributes greater pharmacologic activity despite the fact that the plasma concentrations of R-oxybutynin are lower than S-oxybutynin after administration of racemic drug formulations.[20]

You state that, after administration of a drug product, because of different transit times and site-specific metabolism, there could be differences in the plasma concentrations of the R-enantiomer in different oxybutynin drug products. You maintain that such differences could affect the efficacy of the products and patients' tolerability of the products, so that two products could produce different clinical outcomes.

The authors of the Kachur study you cite suggest that R-oxybutynin has greater antimuscarinic activity than S-oxybutynin in animals. However, the authors of the Kachur study, which included in vivo and in vitro testing, reported that R-oxybutynin and S-oxybutynin had equal effects in depressing potassium chloride-induced contractions of bladder and intestinal muscles. The Kachur study shows that the R-enantiomer of oxybutynin is not necessarily more potent in pharmacological activity compared to the S-enantiomer. The results of these in vitro and preclinical studies you cite do not provide persuasive evidence that R-oxybutynin, the minor enantiomer, is primarily responsible for the safety and efficacy profile of oxybutynin in humans.

To conclude your discussion on this point, you state that the decrease in salivary output and consequent increase in dry mouth severity were correlated with plasma R–desethyloxybutynin concentrations and that no relationship with R-oxybutynin concentrations was observed (Petition at 19). You state that this correlation supports your theory that the untoward effects associated with oxybutynin's tolerability and safety reside primarily with R-desethyloxybutynin concentrations (Petition at 19). Moreover, you state that a 2001 study by Sathyan, Chancellor, et al. shows that both the tolerability and safety of oxybutynin reside primarily with the R-enantiomer of desethyoxybutynin.[21] You describe the study as an evaluation of the concentration-effect relationship between each R-enantiomer and dry mouth. The study was a double-blind, pharmacokinetic/pharmacodynamic study that compared 4 days of dosing with: (1) Ditropan XL 10 milligrams (mg) in the morning, and (2) IR oxybutynin 5 mg in the morning and again 8 hours later. You state that the decrease in salivary output and

---

[19] Kachur JF, Peterson JS, Carter JP. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther* 1988; 247:867-872.

[20] Sathyan G, Chancellor MB, Gupta SK. Effect of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol* 2001; 52:409-417.

[21] Sathyan G, et al., at 409-417.

consequent increase in dry mouth severity were correlated with plasma R-desethyloxybutynin concentrations and that this correlation supports your theory that the tolerability and safety of oxybutynin reside primarily with R-desethyloxybutynin. You acknowledge, however, that this study shows no relationship with R-oxybutynin concentrations and purportedly only shows a relationship with R-desethyloxybutynin. As such, assuming arguendo the data you cite show that R-desethyloxybutynin concentrations correlate with safety and tolerability, this study does not show that primary efficacy and safety activity reside with the minor enantiomer (i.e., R-oxybutynin). R-desethyloxybutynin is the major enantiomer of the metabolite, not the minor enantiomer.

In sum, you have not presented sufficient evidence to support the proposition that the primary safety and efficacy activity resides with the minor enantiomer of oxybutynin (R-oxybutynin). Even if we assume that the scientific evidence shows that R-desethyloxybutynin contributes to what you refer to as the untoward anticholinergic effects associated with Ditropan XL, your arguments are misplaced because R-desethyloxybutynin is what you refer to as the major enantiomer of the metabolite and not the minor enantiomer. Previous studies submitted by ALZA to the NDA support the conclusion that R-desethyloxybutynin is what you refer to as the major enantiomer of the metabolite,[22] and your petition does not dispute this conclusion (Petition at 18). If primary safety and efficacy activity reside with the major enantiomer, we would not expect ANDA applicants to measure the enantiomers individually. The major enantiomer (with which primary safety and efficacy activity resides) comprises a large part of the racemic mixture, so we can reasonably expect that measurement of the racemic mixture would be a scientifically reasonable indicator of the major enantiomer's activity. As discussed above, the BA/BE Guidance developed based on the agency's experience and expertise recommends measurement of individual enantiomers only when four conditions are met, including the condition that primary efficacy and safety activity resides with the *minor* enantiomer.[23] Because Ditropan XL does not meet the third condition outlined in the BA/BE Guidance, the measurement of individual enantiomers is not warranted.

3. *Nonlinear Absorption Has Not Been Shown To Be Present (as Expressed by a Change in the Enantiomer Concentration Ratio with Change in the Input Rate of the Drug) for at Least One Enantiomer*

Although Ditropan XL does not meet the third condition outlined in the BA/BE Guidance and, therefore, measurement of the individual enantiomers is not warranted on that basis alone, we nonetheless considered the fourth condition described in the BA/BE Guidance. Ditropan XL does not meet this fourth condition: that nonlinear absorption be present for at least one enantiomer.

---

[22] See ALZA Clinical Studies C-96-010, C-96-068, C-96-074, and C-97-015.

[23] When primary safety and efficacy resides with the minor enantiomer, the minor enantiomer comprises only a small portion of the total racemic mixture so it is possible that the activity of the total racemic mixture would not be as reliable of an indicator of the minor enantiomer's activity (assuming the three other conditions of the BA/BE Guidance have been met).

The majority of drugs exhibit linear pharmacokinetics, which generally means that the concentration in the blood, serum, or plasma that results from the dose given is proportional to the dose, and the rate of elimination of the drug is proportional to the concentration. Nonlinear absorption can occur when active transport mechanisms responsible for the transfer of a drug into the systemic circulation are saturated. This may happen as the dose or release rate of the drug increases. Nonlinear absorption may be manifested by a nonlinear change in one or more of the pharmacokinetic parameters (e.g., AUC). Generally, in the case of nonlinear absorption, a 10 percent increase in dose would not yield a 10 percent change in drug concentration within the body, but could, for example, result in a 50 percent (or greater) change in drug concentration. Generally, a relatively substantial amount of evidence is needed to reasonably conclude nonlinear absorption is present because other processes (apart from absorption) can also result in a nonlinear change in one or more of the pharmacokinetic parameters. Examples include saturable metabolism and nonlinear elimination. Evidence of nonlinear absorption requires an understanding of the drug substance and how it is absorbed, in addition to studies designed to eliminate other possible causes of nonlinear pharmacokinetics.

In your petition, you state the studies you reference show that nonlinear absorption is present because the enantiomer concentration ratio changes with drug input rate. You state that drug input rate is highly dependent on the formulation and the studies you reference show that that it is important that bioequivalence of individual enantiomers be determined. The studies you reference in apparent support of your conclusion are discussed below. You have not provided sufficient information upon which we can reasonably conclude that nonlinear absorption is present. In fact, available scientific evidence supports the conclusion that Ditropan XL exhibits linear absorption within the dosing range approved in the labeling (5 mg/day to 30 mg/day).

You cite in your petition Study C-96-068, which was submitted in the NDA and reviewed by FDA. This study suggests that absorption of the enantiomers is linear within the approved dosing range (i.e., the enantiomer concentration ratio does not change), and contradicts your conclusion of nonlinear absorption. This study assessed the effect of dose and release rate (IR vs. controlled release) on nonlinear absorption of the enantiomers comparing the R-to-S AUC_{INF} ratios for oxybutynin and desethyloxybutynin.[24] The R-to-S C_{MAX} ratios you state were also approximated in the study. Oxybutynin was administered at 10- and 20-mg doses, controlled release and immediate release, respectively. Ultimately, the mean R-to-S AUC_{INF} ratios did not show a statistically significant difference in values for either oxybutynin or desethyloxybutynin. This study shows that different doses and different formulations of drug administered with varying input rates had no impact on the R-to-S concentration ratios, when treatments were administered at the same time. You also acknowledge that the results indicate that the dose of oxybutynin when administered as tablets with the same in vitro and in vivo release rates did not affect the R-to-S concentration ratios of the

[24] ALZA Clinical Study Report C-96-068.

enantiomers (Supplement at 13).[25] This study not only contradicts your claim of nonlinear absorption, but also supports the conclusion that absorption is linear.

In addition, the Clinical Pharmacology/Biopharmaceutics reviewer of the original Ditropan XL NDA (NDA 20-897) also reported in the review that the R-to-S ratio of oxybutynin to desethyloxybutynin was ***not*** "significantly different" when comparing Ditropan XL and oxybutynin IR. This statement suggests that when there is difference in input rate such as that between an ER and an IR product (which is even greater than that which would be expected when comparing two products with the same dosage form) the R-to-S concentration ratios of oxybutynin to desethyloxybutynin are not significantly different. This lack of difference provides further support that absorption is actually linear within the approved dosing range.

The information above is consistent with the information in the Pharmacokinetics Section of the current product labeling for Ditropan XL. The current approved labeling states that pharmacokinetic parameters for oxybutynin and desethyloxybutynin (C_{MAX} and AUC) are dose proportional. The approved labeling makes no mention of any nonlinear pharmacokinetic process, including absorption.

As discussed above, the available scientific evidence supports the conclusion that Ditropan XL exhibits linear absorption within the approved dosing range. The other studies you cite in your petition, as discussed below, do not provide a reasonable basis upon which we can reasonably conclude otherwise (i.e., that absorption is nonlinear).

A pharmacokinetic study by Zobrist et al., performed in 2001, compared a 5-mg IR tablet with metabolite-to-parent ratios of the R-enantiomers for C_{MAX} and AUC_{INF} of about 8.9 and 21.5, respectively, and ratios for the S-enantiomers of 3.3 and 8.3, respectively, with a transdermal patch that had metabolite-to-parent ratios of the R-to-S enantiomer for the C_{MAX} and AUC_{INF} that ranged from 0.8 to 1.0.[26] You assert that because the Zobrist study shows marked differences in metabolite-to-parent concentration ratios for the IR tablet versus the transdermal patch, the result is a demonstration of the presystemic gut-wall oxidation by CYP3A4 isoenzymes and the stereoselective metabolism of the R–enantiomer (Supplement at 17).

The Zobrist study does not provide persuasive evidence of nonlinear absorption because purported differences in bioavailability between the R- and S-enantiomers of the parent and metabolite between the tablet and the patch are not necessarily indicative of absorption, but rather are likely related to differences in metabolism and presystemic elimination associated with differences in the products' route of administration. Further, even if stereoselective metabolism is present as you claim and results in a lower concentration of one enantiomer, stereoselective metabolism is a type of metabolism not

[25] In addition, your explanation of the same in vitro and in vivo rates is not well supported, given that you have not submitted any data to show a correlation between in vitro results and in vivo performance.

[26] Zobrist RH, Schmid B, Feick A, et al. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutiynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharmaceut Res* 2001; 18:1029-1034.

necessarily indicative of absorption. Stereoselective metabolism does not provide evidence of non-linear absorption.[27]

You state that ALZA Study C-96-074-02 shows that the R-to-S AUC_{INF} ratios for both oxybutynin and desethyloxybutynin were greater ($p<0.001$) for 15 mg of IR oxybutynin (one 5-mg tablets every 4 hours), compared to 10 mg of ER oxybutynin (two 5-mg tablets at once). You also observe that in the ALZA Study C-98-041, 10 mg of oxybutynin was given to patients for 4 days as one 5-mg IR tablet every 8 hours or one 10-mg ER tablet. You indicate that this study showed statistically significant differences ($p<0.001$) in mean values of the R-to-S AUC_{0-24} ratios for oxybutynin and desethyloxybutynin. You state that ALZA Studies C-96-074-02 and C-98-041 demonstrate that the drug input rate of the enantiomers illustrates that the R-to-S AUC_{INF} and AUC_{0-24} ratios for oxybutynin and desethyloxybutynin prove nonlinear absorption. These studies are also not persuasive because (among other reasons) the dosing schedules were different for different treatments, which may have confounded the results.

Although you state that the above studies show that nonlinear absorption is present because the enantiomer concentration ratio changes with drug input rate and drug input rate is highly dependent on the formulation, the studies you reference do not provide persuasive evidence of nonlinear absorption.[28] As stated above, nonlinear absorption may occur when the R-to-S concentration ratios that result from the *dose* administered are not proportional to the actual dose given. This observation was not supported, however, in any of the Ditropan XL studies you reference. In addition, as you concede, the analyses you conducted were post hoc analyses of pharmacokinetic data from Studies 96-074-02, C-98-041, and C-96-068 (Supplement, at 12). As stated above, a relatively substantial amount of evidence is needed to reasonably conclude nonlinear absorption is present because other processes (apart from absorption) can also result in a nonlinear change in one or more of the pharmacokinetic parameters. After careful review of the currently available scientific information, we cannot reasonably conclude that the studies you reference provide a reasonable basis upon which to conclude that Ditropan XL demonstrates nonlinear absorption (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of its enantiomers.[29] In fact, the available scientific evidence supports the conclusion that

---

[27] Id., at 1033. We note that even the authors acknowledge that "[a]dditional clinical results will be required to confirm these relationships."

[28] Further, we note that an analysis resulting from a comparison of an IR oxybutynin formulation to an ER oxybutynin formulation is not relevant to the ranges of input anticipated for ER oxybutynin formulations which may be shown to be bioequivalent. Bioequivalence studies of oxybutynin, in which the 90 percent confidence intervals for C_{MAX} ratios were contained entirely within the bounds of 0.80 to 1.25, would be expected to detect such a difference in absorption. You do not provide any data showing that an ER oxybutynin product meeting all applicable FDA requirements and recommendations for bioequivalence would produce R-to-S ratios different from those of the RLD.

[29] You also claim that the distribution of enantiomers does not appear to be affected by postabsorption mechanisms because the inversion of the S-enantiomer of both oxybutynin and desethyloxybutynin does not occur in vivo (Supplement at 17) (Koch at A142). In the Koch study, only S-oxybutynin (5 to 320 mg) was dosed in healthy men and women, and neither R-oxybutynin nor R-desethyloxybutynin was detected in

Ditropan XL exhibits linear absorption within the approved dosing range. In sum, Ditropan XL does not satisfy the fourth condition listed in the BA/BE Guidance.

Because you have not shown that Ditropan XL meets all the conditions that form the basis for recommending measurement of S- and R-enantiomers individually, we deny your request to require the application of bioequivalence criteria to the enantiomers of oxybutynin and desethyloxybutynin. However, as noted above, we intend to look at metabolite data as supportive evidence of comparable therapeutic outcome.

D. Effect of the Drug Delivery System on the R- and S-Enantiomers

You state that for oral dosage forms, stereoselective metabolism of racemic oxybutynin decreases the bioavailability of R-oxybutynin so that its concentration is lower and that of R-desethyloxybutynin is higher than those of the S-enantiomers. You state that release profiles and delivery technologies can further alter the relative concentrations of metabolite and parent drug for both enantiomers because of site-specific metabolism in the gastrointestinal tract. In essence, you suggest that your ER technology and delivery system uniquely produce varied concentrations of the metabolite and parent drug within the body. You indicate that this would be important to consider when evaluating different ER oxybutynin products because R-oxybutynin compared with S-oxybutynin is primarily responsible for the anticholinergic effects that contribute to clinical efficacy and safety, and R-desethyloxybutynin compared with R-oxybutynin is primarily responsible for the untoward anticholinergic effects that contribute to tolerability and safety.

You maintain that the differences in the concentrations of the metabolite and parent in oxybutynin products will affect treatment outcomes because the drug may cause varying degrees of adverse effects in different patients. Further, you state that with Ditropan XL, the doses can be adjusted downward if intolerable anticholinergic effects, such as dry mouth, blurred vision, dizziness, and constipation, emerge.

A study performed in 1997 by Waldeck et al. suggests that the differences in side effects between oral and intravesical (within the bladder) administration of Ditropan XL may be related to the distribution of the drug in the body and access to the relevant receptors rather than differences in the concentrations of metabolite and parent in oxybutynin products.[30] The Waldeck study authors conclude that:

---

plasma. Because pharmacokinetic dosing of only R-oxybutynin has not been conducted, you state that it is unknown whether the R-configuration of either the parent or metabolite of Ditropan XL inverts to the S-enantiomer. The information you provide is descriptive in nature and, again, offers no additional evidence of nonlinear absorption.

[30] Waldeck K, Larsson B, Andersson, KE. Comparison of oxybutynin and its active metabolite, N-desethyloxybutynin, in the human detrusor and parotid gland. *J Urol* 1997; 157:1093-1097.

> The oxybutynin metabolite, N-desethyl-oxybutynin[31], has similar antimuscarinic activity as its parent compound in the human detrusor. Furthermore, both compounds have similar receptor binding characteristics in human detrusor and parotid gland, respectively. Most likely, N-desethyl-oxybutynin contributes to the therapeutic effect when oxybutynin is used for treatment of the overactive detrusor. It seems reasonable to assume that differences between oxybutynin and N-desethyl-oxybutynin in distribution and access to the relevant receptors, rather than differences in antimuscarinic actions, are mainly responsible for the difference in side effects seen between oral and intravesical administration of oxybutynin.

Because any approved generic versions of Ditropan XL that are therapeutically equivalent to Ditropan XL will be an orally administered ER formulation, we do not believe issues regarding varying treatment outcomes for different dosage forms are relevant to affect a decision of whether to apply bioequivalence criteria to the active metabolite of Ditropan XL. Nor have you provided persuasive evidence that different ER oxybutynin products that use varying drug delivery technologies will produce different effects that will contribute to a different efficacy or safety profile for oxybutynin. FDA would approve a generic Ditropan XL only if the generic product can demonstrate bioequivalence to Ditropan XL as well as meet other relevant statutory and regulatory standards for approval.

III. CONCLUSION

For the reasons discussed above, your petition is denied in part and granted in part. FDA asks ANDA applicants for a generic Ditropan XL to measure the levels of oxybutynin and its active metabolite in both fed and fasting states based on currently available scientific evidence. Based on the currently available scientific evidence, however, FDA does not intend to ask ANDA applicants to apply the standard bioequivalence criteria to the active metabolite, desethyloxybutynin, nor does FDA intend to ask ANDA applicants to apply bioequivalence criteria separately to the enantiomers of oxybutynin or desethyloxybutynin.

Sincerely,

11.05.05

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research

[31] We note that "N" in "N-desethyl-oxybutynin" does not refer to the chiral properties of the compound (i.e. R or S), but rather to the chemical structure.