Dear Mr. Clissold:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or the Agency) on August 5, 2009 (Petition), on behalf of Mallinckrodt, Inc., and its related company, Tyco Healthcare Group LP (collectively Mallinckrodt or Petitioner). We have carefully reviewed the information and arguments presented in the petition. For the reasons explained in the discussion that follows, we conclude that you have not provided adequate evidence to support any of the actions requested in the petition, and your petition is denied.

I. INTRODUCTION

Your petition raises concerns about appropriate methods for demonstrating that generic temazepam products are bioequivalent to Mallinckrodt’s Restoril (temazepam) Capsules USP (7.5 milligrams, 15 mg, 22.5 mg and 30 mg) (Restoril). In essence, you contend that Restoril’s specific onset and release profile is so closely associated with its clinically demonstrated safety and efficacy that a generic product having significantly different onset and release characteristics could also be less (or differently) effective and/or pose significantly greater risk of adverse effects. You therefore argue that generic temazepam products should be considered bioinequivalent to Restoril unless they demonstrate the same onset and release profile, as determined by criteria specified in the petition.

Although the petition asks for action with respect to “all generic temazepam products,” it is primarily concerned with the ANDA for temazepam 7.5 mg capsules submitted by Mutual Pharmaceuticals, Inc. (Mutual), referred to in this response as the “Mutual ANDA.” As surmised in the petition, approval of the Mutual ANDA was imminent when the petition was submitted, and the product has since been approved.1 With respect to this product, you state broadly that temazepam in the 7.5 mg strength “may be particularly sensitive to manufacturing and formulation differences that could affect its

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1ANDA 78-581, approved September 8, 2009.
pharmacokinetic profile and thus its clinical safety and efficacy. More specifically, you contend that the Mutual product is not bioequivalent to Restoril because a significantly greater specific surface area (SSA) of its active ingredient causes it to have a faster onset of action, different clinical profile, and greater safety risks compared to Restoril.

Finally, the petition contends that "a bioequivalence determination based solely on the criteria described in the FDA’s April, 2009 draft guidance on temazepam cannot reveal whether a product has significantly different absorption and release profiles, and thus cannot predict clinical equivalence." You assert that a generic product with a pharmacokinetic profile that is not similar to that of Restoril could not be approved because it would be misbranded. Accordingly, you ask FDA to (1) revise the draft guidance to include additional criteria set forth in the petition; and (2) require all ANDA applicants to show bioequivalence under the new guidance; or, alternatively, to classify all generic temazepam products as bioinequivalent to Restoril ("BX" or "BP") in FDA’s List of Approved Drug Products with Therapeutic Equivalents (the Orange Book).

II. BACKGROUND

A. Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the current abbreviated new drug application (ANDA) approval process for generic drug products. The showing that must be made for an ANDA to be approved is different from what is required in a new drug application (NDA). An NDA applicant must prove that the drug product is safe and effective. An ANDA applicant does not have to prove the safety and effectiveness of the drug product because an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on this finding, however, an ANDA applicant must demonstrate, among other things, that its generic drug product is bioequivalent to the reference listed drug. The scientific premise underlying the Hatch-Waxman Amendments is that drug products that are bioequivalent and pharmaceutically equivalent...
and, therefore, therapeutically equivalent, may be substituted for each other. A generic
drug product is bioequivalent to the reference listed drug 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.
21 U.S.C. 355(j)(8)(B)(i); see also 21 CFR 320.1(e) and 320.23(b).

FDA bioequivalence regulations at 21 CFR part 320 (the “BE regulations”) establish
acceptable methodologies for demonstrating the bioequivalence of pharmaceutically
equivalent drug products. The procedures and principles outlined in the regulations
provide FDA with considerable flexibility in determining the specific test methods and
analytical criteria required to establish bioequivalence for particular drug products or
product classes. 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

Detailed guidance for designing, conducting, and evaluating the results of in vivo
bioequivalence studies are set forth in the BE regulations and in the preface to the Orange
Book.6 The standard bioequivalence (pharmacokinetic) study is conducted using a two­
treatment crossover study design in a small number of volunteers, usually 24-36 healthy
normal adults. Volunteers are normally tested while fasting, unless a fed study is also
desirable (e.g., for drugs with known or potential food effects). Single doses of the test
and reference drug products are administered to these volunteers, and the blood, plasma,
or serum levels of the drug are measured over time. The pharmacokinetic parameters
characterizing the rate and extent of absorption are examined by statistical procedures.
The pharmacokinetic parameters of interest are the area under the plasma concentration
vs. time curve (AUC) calculated to the last measured concentration time (AUC₀₋₉₀), AUC
extrapolated to infinity (AUC∞), which represents the extent of absorption of the drug,
and the maximum or peak drug concentration (Cmax). Cmax is affected by the rate of
absorption and is considered to be a surrogate for the rate of absorption.

The statistical methodology for analyzing these bioequivalence studies is called the two
one-sided test procedure. Two situations are tested with this statistical methodology.
The first of the two one-sided tests determines whether a generic product (test), when
substituted for a brand-name product (reference), is significantly less bioavailable. The
second of the two one-sided tests determines whether the reference product, when
substituted for the test product, is significantly less bioavailable. Based on the opinions
of FDA medical experts, a difference of greater than 20 percent for each of the above
tests has been determined to be significant and, therefore, undesirable. Numerically, this
is expressed as a limit of test-product average/reference-product average of 80 percent for
the first statistical test and a limit of reference-product average/test-product average of 80
percent for the second statistical test. By convention, all data are expressed as a ratio of

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6The description of standard bioequivalence testing is taken generally from the Orange Book at ix-x.
the average response (AUC and C<sub>max</sub>) for test and reference, so the limit expressed in the second statistical test is 125 percent (reciprocal of 80 percent).

For statistical reasons, all data are log-transformed prior to statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90 percent confidence interval for both C<sub>max</sub> and AUC. Because the mean of the study data lies in the center of the 90 percent confidence interval, when the confidence interval falls within the 80-125% acceptance criterion, the ratio of the means of the data for the test and reference products is usually close to 100 percent (a test/reference ratio of 1).

The pharmacokinetic parameter T<sub>max</sub> is defined as the time to peak plasma drug concentration following dosing. T<sub>max</sub> is also used as a general index of the rate of drug absorption. T<sub>max</sub> can be statistically analyzed by nonparametric methods but, due to the highly variable nature of T<sub>max</sub> data, this parameter cannot be analyzed by the same ANOVA methodology used to construct the 90 percent confidence intervals. Differences in T<sub>max</sub> are evaluated qualitatively. Although statistical criteria are not applied, we evaluate differences in T<sub>max</sub> to determine whether they are clinically meaningful.

B. Restoril and Generic Temazepam Products

Restoril was originally marketed prior to 1962, when the Act was amended to require proof of efficacy as well as safety for approved new drugs. Accordingly, it was reviewed under the Drug Efficacy Study Implementation program (DESI), and ultimately was found effective for its current indication. Restoril is the designated RLD for generic temazepam products at all marketed strengths. Multiple generic temazepam products in the 15 mg and 30 mg strengths have been on the market since the late 1980s. The only 7.5 mg generic temazepam approved to date is the Mutual product at issue in the petition, which was approved on September 8, 2009; a separate ANDA for a 22.5 mg generic temazepam product (also submitted by Mutual) was approved on September 14, 2009.

Temazepam is a sedative-hypnotic benzodiazepine agent used for the short-term treatment of insomnia (generally 7 to 10 days). It is generally prescribed for the short-term treatment of sleeplessness in patients who have difficulty maintaining sleep. Temazepam has anxiolytic (anti-anxiety), anti-convulsant, and skeletal muscle relaxant properties. As described in the approved package insert, Restoril was found to be effective in controlled clinical sleep trials comparing Restoril with placebo at the 7.5 mg,

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7 The original dosage strength was 30 mg; additional lower strengths were added through supplemental NDAs over the years.

8 ANDA 78-581. Center for Drug Evaluation and Research scientists reviewed the allegations made in the petition prior to approving the ANDA and did not find any basis in the petition or Agency files to deny or delay approval.

9 ANDA 71-175.
15 mg, and 30 mg strengths. Standard sleep parameters evaluated in the studies included total sleep time, sleep latency (time to effect), REM sleep, number and timing of awakenings, and residual medication effects ("hangover").

The WARNINGS and PRECAUTIONS sections of the approved labeling for Restoril and generic temazepam products provide detailed information about several important safety issues that are highlighted in your citizen petition. In particular, patients taking temazepam should not use alcohol, which can intensify the risk of oversedation as well as potential behavioral abnormalities such as "sleep-driving" (i.e., driving a car or performing other complex tasks while not fully awake, often with no memory of the event). Because the risk of developing oversedation, dizziness, confusion, and/or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients, 7.5 mg of temazepam is recommended as the initial dose for such patients. Finally, in common with other benzodiazepines, Restoril is a controlled substance in Schedule IV under the Controlled Substances Act of 1970 (CSA) (21 USC 811), as reflected in the product’s approved labeling.

C. Current and Proposed Bioequivalence Requirements for Temazepam

Bioequivalence testing requirements for temazepam products are set forth in the draft temazepam guidance, which was issued in April, 2009. While only recently formalized as guidance, these requirements have been applied by FDA for more than two decades. With respect to in vivo testing, the guidance calls for ANDA applicants to submit evidence showing bioequivalence to Restoril capsules (30 mg) in two standard single-dose crossover studies (one fasting and one fed). In vivo testing for strengths other than 30 mg may be waived based on (i) acceptable bioequivalence studies on the 30 mg strength, (ii) proportional similarity of the formulations (both active and inactive ingredients) across all strengths, and (iii) acceptable dissolution testing of all strengths. This position is consistent with the Agency’s general approach to bioequivalence determinations for similarly formulated drugs (including other benzodiazepine drugs) under FDA guidance for industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (BA/BE guidance).

Your petition contends that Restoril has a unique and specific pharmacokinetic profile that generic products must replicate to “help ensure [that] the products are therapeutically equivalent” Petition at 2. You identify release characteristics (speed of onset and a biphasic decline in blood levels) as factors that are especially important to the clinical

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11The Draft Guidance also provides recommendations for dissolution testing and sampling times.

effects, side effect profiles, and abuse profiles of sleeping aid drugs.\textsuperscript{13} You further submit that AUC and $C_{\text{max}}$ are inadequate to demonstrate bioequivalence for temazepam because they do not capture such effects.\textsuperscript{14} You therefore ask FDA to modify the draft temazepam guidance to require statistical analysis to show that the generic product is equivalent to the reference formulation in the following respects:

(a) The measurements $[\text{AUCpr}]_1$ and $[\text{AUCpr}]_2$, where $[\text{AUCpr}]_1$ is the partial area under the curve from 0 to $T_{\text{max}}$ and $[\text{AUCpr}]_2$ is the partial area under the curve from $T_{\text{max}}$ to 8 hours
(b) The ratio of $C_{\text{max}}$ to $T_{\text{max}}$
(c) The absorption rate constant $k_a$
(d) Initial phase ($\alpha$) and terminal phase ($\beta$) half-lives (based on pharmacokinetic analysis)
(e) Time to reach peak concentration ($T_{\text{max}}$)

Your petition suggests that these criteria will specifically address the concerns you have raised with respect to biphasic release profiles, surface area of the active ingredient, and abuse potential.\textsuperscript{15}

III. BASIS FOR DENYING THE PETITION

We have carefully considered the arguments and evidence presented in your petition, and the petition is denied in all respects. You have failed to provide persuasive evidence that the additional criteria you propose are necessary to ensure that generic temazepam products are therapeutically equivalent to Restoril. As there is no basis for adopting the proposed criteria, there also is no need for us to modify the Draft Temazepam Guidance or to change the Orange Book Classifications of generic temazepam products as you request.

Your petition asks FDA to take regulatory action affecting all generic temazepam products on the basis of asserted facts and conclusions about the pharmacokinetic characteristics of Restoril and generic temazepam products. Under the Act and FDA regulations, however, a generic drug product and its RLD are both permitted and expected to differ in various ways that can affect pharmacokinetic performance, such as active ingredient sources/specifications, inactive ingredients, and manufacturing methods. Accordingly, the vast majority of generic drug products are neither expected nor required to match the “precise pharmacokinetic profile” of their reference drugs in order to be considered bioequivalent.\textsuperscript{16}

\textsuperscript{13}Petition at 7-8.
\textsuperscript{14}Petition at 10.
\textsuperscript{15}Petition at 10.
\textsuperscript{16}See, e.g., FDA-2001P-0155-0004 (available online at http://www.regulations.gov) (denial of citizen petition requesting additional bioequivalence criteria based on asserted pharmacokinetic differences). In very rare instances we have required additional bioequivalence criteria including various pharmacokinetic
The pharmacokinetic characteristics of Restoril that you point out in the petition are well known to FDA and have been since long before the draft temazepam guidance was issued. They do not distinguish temazepam from other immediate-release dosage forms including other benzodiazepine drug products, nor do they provide any basis for concern about the potential safety, effectiveness, or abuse potential of generic temazepam products approved under the existing bioequivalence guidelines.

In particular, you have provided no evidence from clinical trials, pharmacokinetic studies, bioequivalence testing, or any other source that demonstrates the asserted relationship between Restoril’s specific onset and release characteristics and its clinical safety or efficacy. Instead, the petition relies entirely on uncorroborated generalities and theoretical speculation to support this critical point. The same is true of your assertions that generic products with differing onset and release profiles may be less safe or effective or more prone to abuse and diversion than Restoril. For us to adopt the additional measures you recommend as essential to bioequivalence for generic temazepam products, you would need to provide evidence showing that differences in the parameters to be assessed correlate with clinically important differences in a way that is not the case.

Rather than addressing this point directly, the petition merely describes certain pharmacokinetics documented in Restoril’s approved labeling and NDA file, points out various ways in which they might rationally contribute to clinical performance, and assumes that because the product has been shown to be clinically safe and effective, its distinct pharmaceutical profile must also be clinically significant. This is not the case.

See, e.g., Petition at 1-2 (offering generalized discussion of pharmacokinetic factors as they relate to the “goals” of safe and effective sleep aid drugs as reason for a claim that “it is essential that the overall pharmacokinetic characteristics of generic temazepam products be similar to Restoril”); Petition at 8 (pharmacokinetic characteristics of Restoril described as “predicting,” “responsible for,” or “important to” clinical performance characteristics); Petition at 11 (Restoril’s “unique and specific pharmacokinetic profile . . . is associated with, and likely responsible for, its clinical profile”).

See, e.g., Petition at 2 (“there are significant questions concerning the potential for food effect or alcohol dose dumping to be significantly different depending on the physical characteristics of both the [generic] drug and the drug product”) (“A generic temazepam product that had a different onset of action and/or a different late effect than [Restoril] could pose a significant safety risk to patients); Petition at 4 (“As FDA is aware [an asserted large increase in surface area] could also have a dramatic impact on in vivo bioavailability . . . in the presence of food and/or alcohol”); Petition at 8 (fall risks in elderly patients “could be greatly increased by even a small increase in the rate of onset of action of a generic version of Restoril); Petition at 9 (“a change in either the bioavailability or pharmacokinetic profile of the 7.5 mg strength may have a particularly harmful effect on elderly and debilitated patients”).

Petition at 8 (generic temazepam products with “even a slightly faster onset of action . . . would presumably increase the risks of abuse and diversion” because “[i]t is well known that drugs with a rapid onset of action are more likely to be abused and misused”). We note that Restoril is a Schedule IV drug under the CSA, and any generic temazepam product would have the same status and corresponding labeling concerning drug abuse and diversion risks.
not captured by differences in AUC and C\textsubscript{max}. The petition fails to provide, nor are we aware of, any such evidence.

The only allegedly new information in the petition is the asserted two-fold difference in the surface area of the active ingredient in Mutual’s 7.5 mg generic product compared to Restoril. Surface area is a physicochemical characteristic that commonly differs between different manufacturers’ versions of the same drug substance. Acceptable surface area ranges specified in individual NDAs and ANDAs are carefully examined by FDA reviewers, and must be maintained thereafter by compliance with current good manufacturing practices. FDA is aware that the particle size and surface areas of the active ingredients of these products do differ, but relies on bioequivalence testing that shows that those parameters do not affect the bioavailability of the drug. If the two products are bioequivalent (and the ANDA otherwise meets the requirements for approval), the clinical effects of those products can be expected to be the same.

You have not provided evidence, such as in vivo data from pharmacokinetic studies or safety or efficacy studies, to demonstrate that this difference is in fact relevant to clinical performance, or that it would in any way affect the products’ clinical efficacy, safety, or potential for abuse or diversion.\textsuperscript{21} Our review of relevant data in Agency files likewise fails to support the suggested link between surface area and speed of onset. You also fail to provide any evidence at all about the existence, extent, or significance of surface area variations for any other generic temazepam products at any dosage strength.

FDA continues to believe that AUC and C\textsubscript{max}, supported by T\textsubscript{max}, are adequate to establish bioequivalence for generic temazepam drug products. If a drug is both pharmaceutically equivalent and bioequivalent to the listed drug it references, it is considered therapeutically equivalent and therefore substitutable. The scientific premise underlying the Hatch-Waxman Amendments is that when other aspects of the drug products (e.g., active ingredient, strength, dosage form, labeling) are the same, bioequivalent drug products may be substituted for each other.

Finally, we reject your argument that FDA should designate temazepam generic products in the Orange Book using the code BP or BX.\textsuperscript{22} A BP code applies to a drug that presents a potential bioequivalence problem until adequate in vivo bioequivalence data are submitted. That would not apply to any temazepam product that FDA would approve, because FDA will require adequate in vivo bioequivalence data as a basis for that approval. The BX code applies to drug products for which the data reviewed by FDA are not sufficient to determine therapeutic equivalence. Again, that would not apply to any

\textsuperscript{21}For instance, SSA is claimed to be “important to the clinical performance” of Restoril 7.5 mg capsules based on a statement in one of Mallinckrodt’s patents that a capsule product with a specified particle size and surface “is effective in the treatment of insomnia” (Petition Attachment 7, cited in Petition at 9 and note 8.) Transcripts submitted from related patent litigation proceedings also fall short as proof that SSA differences are significant to bioequivalence (Petition at 4 and nn 2-5). In fact, the discussion of SSA in that proceeding was in the specific context of technical infringement issues, not bioequivalence.

\textsuperscript{22}Petition at 7.
temazepam product approved under an ANDA, because FDA will not approve such a product in the absence of evidence of pharmaceutical equivalence and bioequivalence, which together demonstrate therapeutic equivalence.\textsuperscript{23}

IV. CONCLUSION

For the reasons detailed above, we disagree that the actions requested in your petition are necessary to ensure the clinical safety, effectiveness, or bioequivalence to Restoril of generic temazepam products. FDA has determined that the Mutual product and other approved generic temazepam products in different dosage strengths have been shown to have the same active ingredient, strength, dosage form, and route of administration, and to be bioequivalent to Restoril using appropriate measures outlined in the draft temazepam guidance. As such, they are appropriately rated as therapeutically equivalent to Restoril, and we would expect that the clinical effects of those products would be the same. Accordingly, your petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

\textsuperscript{23}FDA would not apply BP or BX codes to any generic product that it was approving under the 1984 Hatch-Waxman Amendments, as all such generic products must satisfy bioequivalence requirements. These codes have been primarily applied to generic products that were approved prior to the 1984 amendments.