February 5, 2010

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Attn: Ms. Gloria Ortega

Re: Citizens Petition Regarding Extended-Release Morphine Sulfate Drug Products

Dear Ms. Ortega:

Pursuant to our telephone conversation yesterday, please find enclosed an original and four (4) copies of a Citizen Petition submitted today on behalf of Actavis Elizabeth LLC regarding extended-release morphine sulfate drug products. Pursuant to our telephone conversation, we have enclosed three (3) sets of exhibits referenced in the Citizen Petition.

Thank you for your attention to this matter.

Sincerely,

Donald E. Segal

Enclosures

cc: Gary J. Beuhler, R.Ph., Director, Office of Generic Drugs (without exhibits)
Bob A. Rappaport, M.D., director, Division of Analgesics, Anesthetics and Rheumatology Products (without exhibits)
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CITIZEN PETITION


I. Actions Requested

Actavis requests that the Commissioner of Food and Drugs and the U.S. Food and Drug Administration (FDA) take the following actions with respect to all Abbreviated New Drug Applications (ANDAs) seeking approval of extended-release morphine sulfate drug products and citing KADIAN® (morphine sulfate extended-release) capsules as the reference listed drug (RLD):

- Ensure that bioequivalence determinations be based upon data demonstrating equivalent plasma concentration levels across the entire dosing interval, including at key time intervals and at the same dosage strength as the RLD;

- Ensure that bioequivalence determinations be based upon data demonstrating equivalent time to the maximum drug concentration (T_{max});
Ensure that applicants provide in vitro dissolution and in vivo test data for all proposed strengths to assess dose-dumping risks, if FDA determines that the proposed product raises toxicity or efficacy concerns; and

Ensure that bioequivalence determinations for ANDA candidates seeking approval at the multiple dosage strengths of KADIAN be based upon data demonstrating bioequivalence using KADIAN comparators at the 10 mg and 200 mg dosage strengths, in addition to the 80 mg or 100 mg dosage strengths, as each utilizes a different pellet formulation.

II. Statement of Grounds

1. Background Information

Actavis Elizabeth LLC ("Actavis") holds the approved New Drug Application (NDA) for KADIAN (morphine sulfate extended-release) capsules, which it acquired from Alpharma Inc. in 2008.1 Currently, extended-release oral capsules of KADIAN are approved by FDA for marketing in eight varying strengths, ranging from 10 mg to 200 mg. The KADIAN formulation consists of a gelatin capsule containing polymer-coated morphine sulfate pellets. Note that the same pellet formulation is not used in each capsule strength. Instead, three different pellet formulations exist, only one of which is found in each dosage strength. Each pellet is comprised of an inert sugar core, surrounded by a morphine sulfate binder layer, and covered in an extended-release pH-dependent polymer-coated pellet technology.2 Following administration and dissolution of the capsule, the pellets are released into the digestive system.3

Experts in the field concur that there is an important place in the market for long-acting morphine sulfate products in managing moderate to severe pain in patients. KADIAN was not the first morphine sulfate extended-release first approved for marketing. Several other extended-release morphine sulfate products are approved for use in the marketplace, most of which pre-date the market entry of KADIAN. FDA approved MS CONTIN®4 (morphine sulfate extended-release tablets) in 1987 and ORAMORPH SR®5 (morphine sulfate extended-release tablets) in 1991, and AVINZA®6 (morphine sulfate extended-release capsules) in 2002. Inter-patient variability occurs with all morphine products. Some earlier generation morphine sulfate products produce

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1 See NDA #020616, Approved July 3, 1996.
4 MS Contin is a registered trademark of Purdue Pharma L.P.
5 Oramorph SR is a registered trademark of Xanodyne Pharmaceuticals, Inc.
6 Avinza is a registered trademark of King Pharmaceuticals, Inc.
consistent serum levels over extended periods of time. Some later products with more complex pharmacokinetic profiles, including KADIAN, have adopted this approach while others, e.g. Avinza, produce a higher initial serum level than that seen in the later hours of the dosing interval. Thus, all of the modified release morphine products do not produce the same serum profile. In addition, note that FDA has approved numerous ANDAs for generic products demonstrating bioequivalence to MS CONTIN. While KADIAN and these other products share the same active ingredient and extended-release method of delivery, these products have pharmacokinetic and clinical differences. As a result, FDA has correctly determined that these products are not therapeutically equivalent to KADIAN.

Experts and clinicians in the field have also recognized the pharmacokinetic distinctions among these products that are further complicated by interpatient variability. One such expert stated in 1998, prior to the entry of newer morphine sulfate products, that:

There are various modified release formulations of morphine with recommended dosage intervals of either 12 or 24 hours. The pharmacokinetics of morphine characterizing these formulations are frequently different as a consequence of the various approaches used to modify the morphine absorption rate. Therefore, formulations cannot automatically be assumed to be bioequivalent in individual patients: the FDA promulgated statistical approach examines average bioequivalence whereas the newer approaches of population or individual bioequivalence may be more relevant.

For example, data examining plasma concentrations have demonstrated that newer market entrant, AVINZA, delivers a higher initial serum level over the course of its time in the body, whereas KADIAN delivers more of a gradual-ascending, gradual-descending dose to the patient. Specifically, KADIAN capsules “contain polymer coated extended-release pellets of morphine sulfate that release morphine significantly more slowly than from conventional oral preparations.” In contrast, the FDA-approved product labeling for AVINZA states that AVINZA is comprised of an immediate release component that “rapidly achieves plateau morphine plasma concentrations and an extended release component that maintains plasma concentrations throughout the 24-hour dosing interval.”

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7 See, e.g., ANDA #074769 (held by AB Generics), ANDA #075295 (held by Endo Pharmaceuticals), ANDA #075407 (held by Clonmel Healthcare), ANDA #076412 (held by Mallinckrodt).
Similarly, with respect to absorption, the extended-release morphine sulfate products on the market each perform differently. For example, the approved labeling for AVINZA states that “morphine concentrations of approximately 3 to 6 mg/ml were achieved within 30 minutes after dosing and maintained for the 24-hour dosing interval.”

For KADIAN, 50% of the morphine absorbed reaches systemic circulation, on average, after 8 hours, with $T_{\text{max}}$ being reached, on average, at 8.6 hours following single-dose administration. While the $T_{\text{max}}$ of AVINZA is not reported in its FDA-approved label, the plasma concentration tables included in the label reflect a plasma concentration curve quite different from that of KADIAN and published studies have noted vastly different $T_{\text{max}}$ values (e.g., 6.7 hours for AVINZA vs. 12.9 hours for KADIAN). In comparison, the MS CONTIN and ORAMORPH SR labels both report that 50% of the morphine absorption occurs, on average, after 1.5 hours in healthy volunteers.

An Australian study of cancer patients reported mean MS CONTIN $T_{\text{max}}$ values of 4.4 hours +/- 2.3 hours and a Canadian study of cancer patients reported mean MS CONTIN XL $T_{\text{max}}$ values of 6.3 hours +/- 2.9 hours. A steady-state study of MS CONTIN in healthy subjects reported mean $T_{\text{max}}$ values of 2.27 hours +/- 0.24 hours. Lastly, a published study of ORAMORPH SR in healthy volunteers noted mean $T_{\text{max}}$ values of 2.5 hours with a median range of 1-4 hours in the first 12 hours following administration.

The distinctive single-administration plasma concentration curves found in the newer generation morphine sulfate extended-release product labels are as follows:

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12 Ex. 2, KADIAN (morphine sulfate extended-release) capsules Prescribing Information (February 2009).
18 Ex. 12, J. Heinrich-Nols, et al., Bioequivalence Study of Two Morphine Extended Release Formulations after Multiple Dosing in Healthy Volunteers, 37(3) Int. J. of Clinical Pharmacology and Therapeutics 153, 156 (1999) (noting Table 1).
KADIAN

Graph 2 (Study # MOR 9/92): Dose normalized mean steady state plasma morphine concentrations for KADIAN® (once a day), and an equivalent dose of a 12-hour, extended-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours, (i.e., 24).

AVINZA

Graph 1
Mean Steady-State Plasma Morphine Concentrations Following Once-Daily Administration of AVINZA Capsules or 6-Times Daily Administration of Morphine Solution

A once-daily dose of AVINZA provided similar \( C_{\text{max}} \), \( C_{\text{avg}} \), and AUC values and peak-trough fluctuations (% R. \( C_{\text{avg}} \)-\( C_{\text{max}} /C_{\text{avg}} \)) compared to 6-times daily administration of the same total daily dose of morphine oral solution (Table 1).

As an opioid agonist and analgesic, KADIAN is a Schedule II controlled-substance which has an abuse liability similar to other opioid analgesics. Moreover, some extended-release formulations have the potential to dose-dump when in the presence of alcohol, and Actavis fully supports the agency's position that this must be looked at for long-acting products. As a result of the risks associated with dose-dumping and the abuse liability of opioid analgesics, generally, the sponsor carefully studied
KADIAN during its product development and submitted both in vitro and in vivo studies to the agency for review with its marketing application.

2. Bioequivalence Demonstration Must Include Demonstration of Additional Pharmacokinetic Measures Including Mean $T_{\text{max}}$ and Mean Plasma Concentration Levels Across the Entire Dosing Interval, Together With Other Measures Including Across Varying Patient Populations

Actavis requests that any ANDA applicant citing KADIAN as the RLD be required to demonstrate bioequivalence in the clinical performance and efficacy of the product through the same gradual-ascending, gradual-descending release as KADIAN maintains over the entire dosing interval. Because of the unique pellet and other formulation characteristics of KADIAN and the vastly different plasma concentration curves over the same dosing interval between KADIAN and other extended-release morphine sulfate products on the market, any ANDA applicant must be required to show equivalent pharmacokinetic performance throughout the entire span of the dosing interval, as demonstrated by bioequivalent mean plasma concentration across the entire dosing interval and at specific time intervals. In particular, the key time intervals would be in the 0-1 hour, 8-12 hour, and 18-24 time ranges, measuring against the RLD at the same dosage strength. Thus, Actavis requests that FDA require an equivalent pharmacokinetic profile be demonstrated, not only by the traditional pharmacokinetic parameters of $C_{\text{max}}$, AUC$_{0-t}$ and AUC$_{0-\infty}$, but also by the pharmacokinetic parameters of AUC$_{pR}$ and $T_{\text{max}}$.

As stated earlier, plasma concentrations following KADIAN administration differ from plasma concentrations following administration of other morphine sulfate extended-release products due to their individually designed formulations — e.g., KADIAN having a gradual-ascending and gradual-descending release into the system versus immediate-release or bimodal products featuring immediate-release and extended-release components. This performance characteristic is critical in distinguishing KADIAN from other morphine sulfate extended-release products on the market. Significantly, KADIAN capsules are indicated for dosing both every 12 hours and every 24 hours compared to other morphine sulfate extended-release products on the market which provide for only once daily administration or more customized administration every 8 or 12 hours. As such, the disintegration and dissolution rates can and do vary from one morphine sulfate extended-release product to another.

The following plasma concentration graphs for KADIAN demonstrate the differing performance and exposure levels of KADIAN to that of both morphine solution and twice-daily (BID) extended-release morphine tablets. Note the distinctive, gradual-ascending and gradual-descending plasma concentration curve for KADIAN:

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The long-acting nature of KADIAN is not due to intrinsic properties of morphine itself but rather to the rate of release from the pellets as they travel through the gastrointestinal tract. This rate is controlled by the nature of the pores in the polymer shell.20

Moreover, single-dose pharmacokinetic studies have demonstrated that KADIAN capsules provide a longer extended-release profile (reduced $C_{\text{max}}$ and longer $T_{\text{max}}$) than

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morphine sulfate controlled-release tablets (MS CONTIN®)\textsuperscript{21}, a formulation that is indicated for twice-daily dosing\textsuperscript{22}

FDA has stated in its Guidance for Industry on the Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations,\textsuperscript{23} that "[w]here the test product generates plasma levels that are substantially above those of the reference product, the regulatory concern is not therapeutic failure, but the adequacy of the safety database from the test product."\textsuperscript{24} Conversely, FDA states in this Guidance that "[w]here the test product has levels that are substantially below those of the reference product, the regulatory concern becomes therapeutic efficacy."\textsuperscript{25} In addition, FDA states that "[p]roper mapping of individual dose-response or concentration-response curves is useful in situations where the drug product has plasma levels that are either higher or lower than the reference product and are outside usual BE limits."\textsuperscript{26}

As discussed above, KADIAN has a unique pellet formulation and a vastly different plasma concentration curve over the same dosing interval than other extended-release morphine sulfate products. As a result, Actavis requests that any ANDA applicant must be required to show equivalent pharmacokinetic performance throughout the entire span of the dosing interval, as demonstrated by bioequivalent mean plasma concentration across the dosing interval and at specific time intervals. In particular, the key time intervals would be in the 0-1 hour, 8-12 hour, and 18-24 time ranges, measuring against the RLD at the same dosage strength.

Actavis additionally requests that an equivalent pharmacokinetic profile must be demonstrated by any ANDA applicant citing KADIAN as the RLD, not only by the traditional pharmacokinetic parameters of $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, but also by the pharmacokinetic parameters of $AUC_{\text{PR}}$ and $T_{\text{max}}$, since KADIAN is a drug for which early absorption measurements during the first hours following administration are clinically important in determining therapeutic equivalence for the management of moderate to severe pain. FDA’s Guidance providing general considerations for bioequivalence demonstrates states that $T_{\text{max}}$ is among the pharmacokinetic measures that FDA "recommends" for submission.\textsuperscript{27} In addition, FDA has said that in bioequivalence determinations, "$T_{\text{max}}$ may also be evaluated, if rapid onset of effect is necessary for

\begin{itemize}
\item 21 Ex. 13, MS CONTIN® Package Insert, Purdue Pharma LP (2009).
\item 22 Ex. 14, Maccarrone C, West RJ, Broomhead AF, Hodsman GP, Single dose pharmacokinetics of Kapanol\textsuperscript{TM}, a new oral sustained-release morphine formulation, 7 DRUG INVEST 262-74 (1994).
\item 24 \textit{Id.} at 5.
\item 25 \textit{Id.}
\item 26 \textit{Id.}
\item 27 \textit{Id.} at 25.
\end{itemize}
efficacy." While $T_{\text{max}}$ is important in evaluating products having a rapid onset component for clinical efficacy purposes, evaluating $T_{\text{max}}$ is an equally important measure to examine in products like KADIAN which do not have such a rapid onset component where other morphine sulfate extended-release products on the market do have such a component. As such, any successful ANDA candidates should be required to demonstrate this pharmacokinetic property to the required confidence interval.

Although FDA has correctly determined that $T_{\text{max}}$ is an important pharmacokinetic factor in determining therapeutic equivalence, current FDA standards do not account for differences in $T_{\text{max}}$ or the differences in absorption at critical time points during the drug’s release when analyzing bioequivalence. For example, KADIAN and AVINZA would appear to be bioequivalent by current FDA standards (see Figure 1 below) during either a 0-24 hour or 0-60 hour period based on AUC criteria, even though their respective $T_{\text{max}}$ values are very different. Moreover, at critical absorption time points for KADIAN (e.g., AUC$_{0-1}$, AUC$_{8-12}$, and AUC$_{18-24}$), AVINZA demonstrates significantly different plasma concentrations (see Fig 1). Such differences in $T_{\text{max}}$ and absorption result in clinically meaningful differences between these two drugs, but FDA’s standard bioequivalence criteria are not sensitive to prevent a generic extended-release morphine product that has the same plasma profile as AVINZA from appearing bioequivalent to KADIAN.

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29 Ex 17, Actavis, data on file.
30 KADIAN NDA – Clinical Pharmacology and Biopharmaceutics Review (Submitted 1994).
Should FDA not require the additional pharmacokinetic profile parameters discussed above, an ANDA applicant citing KADIAN as the RLD could pass FDA's general standards for bioequivalence, yet not be therapeutically equivalent to the RLD.

These similar issues have been raised in earlier Citizen Petitions31 filed with the agency regarding additional pharmacokinetic measures and considerations which FDA should examine when reviewing ANDA applications. For example, petitioners have asked that FDA consider not only AUC-\(\infty\), and C_{max} but also AUC_{pR} (a more sensitive absorption measure) in reviewing ANDA applications to ensure that products able to meet average bioequivalence metrics but which are unable to provide the same clinical effects as the RLD according to more sensitive pharmacokinetic measures are not deemed therapeutically equivalent.32 FDA has yet to respond in detail to these issues.

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31 For example, a 2007 Citizen Petition by Sanofi-aventis requested that zolpidem drug products seeking to show bioequivalence to AMBIEN CR be required to show equivalence as a function of time such as AUC-\(0,3\), AUC-\(3,6\) and AUC-\(6,\infty\) in addition to traditional bioequivalence parameters. Docket No. 2007P-0224. Ex. 18. While the petition remains outstanding, FDA proposed draft bioequivalence guidance to Zolpidem in August 2009 proposing fed and fast studies looking at specific time intervals. Ex. 19.

32 An earlier filed 2004 Citizen Petition submitted by McNeil Consumer & Specialty Pharmaceuticals ("McNeil") also raised this issue regarding ANDA approvals referencing CONCERTA® (methylphenidate HCl) extended-release tablets. Ex. 20, McNeil Consumer & Specialty Pharmaceuticals Citizen Petition, Docket No. 2004P-0139 (March 19, 2004). McNeil had asked that FDA consider not only AUC-\(\infty\), and C_{max} but also AUC_{pR}, a measure McNeil indicates is more sensitive measure of early and late absorption profiles in extended-release products. Id. at 1-2. AUC_{pR} is the “area under the curve to the population median T_{max} of the reference formulation in a single-dose study in healthy fasting volunteers.” Id. at 1. McNeil presented evidence demonstrating that products able to meet average bioequivalence metrics may fail to provide the same clinical effects under the labeled conditions for use on account of variations in more sensitive pharmacokinetic measures such as AUC_{pR}. McNeil argued that additional measures for...
Actavis requests that the agency not approve any ANDA which is unable to demonstrate the same or similar plasma concentrations as the RLD over the dosing interval, and beyond, to the confidence interval set by FDA. In particular, the agency must scrutinize the pharmacokinetic data of any ANDA applicant to ensure that bioequivalent concentrations are present at key time intervals, such as hourly mean concentrations from 0-1 hours, 8-12 hours, 18-24 hours. The blood concentrations at time points at which re-dosing is likely to occur is particularly important to avoid possible toxic effects of multiple doses of morphine sulfate due to high remaining mean plasma concentration at the time of redosing. (See, for example, the concentration spread between KADIAN and AVINZA at 12 hours in Figure 1 above). The need for such concern and scrutiny is further supported by the acknowledged inter-patient variability, in general, in treatment with certain extended-release opioids.

While FDA has not previously addressed these issues in detail, it has addressed other bioequivalence demonstration concerns including those regarding distinct release mechanisms. While FDA explained to a petitioner that a product’s release mechanism is part of its formulation and does not, by itself, preclude a showing of therapeutic equivalence, the agency clarified that when the release mechanism of a proposed ANDA product has a different feature than the RLD that affects the safety or efficacy of the product, FDA would not approve the ANDA. Actavis requests that FDA carefully consider the safety and efficacy implications respecting any formulation differences for ANDAs referencing KADIAN and require data necessary to ensure bioequivalence and the absence of clinical differences due to formulation differences such as the release mechanism of the KADIAN coated pellets.

assessing bioequivalence must be considered to prevent products that are not clinically equivalent from being deemed therapeutically equivalent. FDA similarly responded indicating that the agency needed extensive review time for the complex issues that McNeil had raised. Ex. 21, FDA Response Letter to McNeil Consumer & Specialty Pharmaceuticals (Sep. 7, 2004).


Ex. 23, In the agency’s May 1, 2009 response to a Citizen Petition filed by Warner Chilcott (US), LLC ("Warner Chilcott"), the company had argued to FDA that a doxycycline hyclate drug product with an outer coating alone should not be considered pharmaceutically equivalent to tablets with coated doxycycline hyclate pellets. FDA explained that the release mechanism of the drug product is part of the formulation rather than dosage form and concluded that products with these various coatings could be therapeutically equivalent dosage forms. However, FDA stated that “If it is determined that the safety or efficacy of a specific drug product proposed for approval in an ANDA is affected because it has an outer coating rather than coated pellets, that ANDA would not be approved.” FDA Response Letter to Warner Chilcott, Docket No. 2008-P-0586 (May 1, 2009), at page 7. FDA went on to state that “To the extent appropriate, FDA will apply these requirements to ANDAs referencing Doryx DR Tablets.” Id.
3. Dose-Dumping Considerations Necessitate Both In Vitro and In Vivo Study

Actavis also requests that FDA require NDA and ANDA applicants for modified release oral dosage form opioid drug products conduct in vitro dissolution tests in the presence of alcohol for all proposed strengths in solutions containing an appropriate range of ethanol (up to 40%) to evaluate the susceptibility of the proposed drug product to alcohol-induced dose-dumping.

It is well known, in the wake of the market suspension of PALLADONETM (hydromorphone hydrochloride extended-release capsules) following discovery of potentially fatal adverse reactions when taken with alcohol, that “dose-dumping” is a concern with respect to extended or modified-release opioid drug products consumed with alcohol. Dose-dumping is a term that describes the unintended, rapid release in a short period of time of the entire or significant amount of the drug contained in a modified-release dosage form. Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a significant risk to patients, either because of heightened safety issues or diminished efficacy or both.

Because some modified-release oral dosage forms contain drugs and excipients that exhibit higher solubility in ethanol-containing solutions compared to water, consumption of alcohol can adversely affect the performance of the modified-release product in the body.

In July 2005, the FDA requested that Purdue Pharma voluntarily suspend sales of Palladone (hydromorphone extended-release capsules), after the FDA reviewed the company’s in vivo ethanol testing data. Those data demonstrated that co-ingestion of PALLADONE with ethanol derived from alcoholic beverages and medications can lead to dose-dumping. The FDA found that elevated levels in the peak plasma concentrations can be lethal, even in opioid-tolerant patients.

To date, dose-dumping in the extended-release opioid drug class has only been reported for PALLADONE. Nevertheless, the labeling of products in that class bear warnings to that effect and manufacturers have studied the effects of product-alcohol interactions. For example, the KADIAN package insert states:

Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics,

37 Id.
antiemetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%.38

Significantly, FDA’s approval of this warning was based on both in vivo and in vitro data submitted by Actavis in its application.39

Sponsors for all modified-release opioids have reportedly been required to study the effect of alcohol on the dissolution of their product in vitro, followed by in vivo testing as needed. While the dissolution of all modified-release opioids was assessed in the presence of 40% alcohol, AVINZA and KADIAN were also studied using 4% and 20% alcohol.40 The results illustrate that each modified-release opioid can have unique properties with respect to the dose-dumping issue. The agency has documented this observation in the past. See, for example, the following discussion in FDA briefing materials for the advisory committee’s consideration of Embeda:

“Avinza showed substantial release of drug within the first hour of dissolution. Kadian had complete drug release once it was placed in a buffer solution containing alcohol. MS Contin and Oramorph SR showed minimal effect of drug release in the presence of 40% alcohol.

Alpharma went on to conduct in vivo testing with alcohol, the results of which showed there was not an increase in drug release in the presence of alcohol. These results superseded those from the in vitro studies.

In October, 2005, language was added to the Avinza label regarding the in vitro alcohol interaction. Wording was added to the Pharmacokinetic section describing the in vitro studies and results, and the following language was added to the Box Warning and throughout the label:

‘Patients must not consume alcoholic beverages while on Avinza therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza therapy. Consumption of alcohol while taking Avinza may result in the rapid release and absorption of a potentially fatal dose of morphine.’41

41 See Ex. 22, Background Materials for Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, November 14, 2008, available at
The foregoing supports two important conclusions: (1) while it is important to study ethanol interaction with each opioid formulation through in vitro testing, it may be equally important to test the product in vivo in the presence of alcohol; and (2) there are degrees of interaction with related degrees of safety risk which cannot be predicted absent such testing. While the AVINZA label, for example, carries a greater safety risk for alcohol dose-dumping, in vivo study of KADIAN has demonstrated a low risk of alcohol-induced dose-dumping with KADIAN.42

As discussed above, Actavis therefore requests that NDA and ANDA applicants for modified release oral dosage form opioid drug products conduct in vitro dissolution tests in the presence of alcohol for all proposed strengths in solutions containing an appropriate range of ethanol (up to 40%) to evaluate the susceptibility of the proposed drug product to alcohol-induced dose-dumping.

The agency has correctly stated that when there are dose-dumping concerns raised by a product, both in vitro and in vivo test results must be examined, and Actavis supports that approach. As such, when an NDA holder has also conducted in vivo testing in support of the ultimately approved labeling, Actavis requests that FDA require all ANDA submitters who rely upon that NDA as the reference listed drug, to conduct appropriate in vivo testing as well. As evidenced by previously discussed differences between newer market entrants, AVINZA and KADIAN, in vivo bioequivalence testing is important to conduct for KADIAN, for example, because there may be differences in formulations, not just active ingredients, which might affect the rate and extent of the drug reaching the primary site of action.

Finally, in support of FDA’s actions already underway, Actavis requests that the results of in vitro and in vivo testing be considered in the evaluation of any NDA or ANDA regarding the required labeling and any need for a REMS.

4. Data Must Demonstrate Bioequivalence At Dosage Strengths Representing Each of 3 Pellet Formulations Used in KADIAN

Due to the different pellet formulations of KADIAN at differing dosage strengths, Actavis requests that FDA ensure the use of appropriate KADIAN comparators in measuring bioequivalence at the respective dosage strengths to accommodate for the potential serum profile impact that each pellet formulation may have.
FDA has issued Draft Guidance on Morphine Sulfate\textsuperscript{43} for extended-release capsules identifying 5 recommended studies for demonstration of bioequivalence. This Draft Guidance takes a one-size-fits-all approach to bioequivalence determinations involving morphine sulfate extended-release capsules. This approach fails to account for the individual nuances of each product: for example KADIAN has specially formulated pellets. These recommended studies waive the need for \textit{in vivo} testing at the 20 mg, 30 mg, 50 mg, 60 mg, and 200 mg dosage strengths provided the applicant supplies acceptable bioequivalence data from studies on the 80 mg and 100 mg strengths (assuming ANDA approval of all of the foregoing dosage strengths are being sought).

KADIAN's formulation at each dosage strength is determined based upon the incorporation of one of three different types of pellets (each varying in strength from a low-dose to a high-dose). Currently, the 80 mg and 100 mg dosage strengths utilize the same pellet formulation. As a result, there are two other pellet formulations present only in the 10 mg and 200 mg formulations, respectively, which an ANDA applicant following FDA's Draft Guidance recommendations would not ordinarily study as comparators. This potentially compromises the reliability of the bioequivalence data that an ANDA applicant would obtain from bioequivalence studies utilizing KADIAN comparators at the 80 mg and 100 mg strengths (or other dosage strengths which utilize unique pellet formulations). Accordingly, appropriate KADIAN comparators for measuring bioequivalence at the respective dosage strengths should be required.

\section{Environmental Impact}

Actavis claims a categorical exclusion from the environmental assessment requirement under 21 C.F.R. § 25.31.

\section{Economic Impact}

Actavis will submit an assessment of the economic impact of the actions requested herein should the Commissioner determine such assessment is necessary in evaluating this petition.

V. Certification

We certify that, to the best of our knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) we have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to us. We further certify that the information upon which we have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: November 17, 2009. We received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, from the following persons or organizations: Actavis Elizabeth LLC. We verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

[Signature]
Donald E. Segal
Julie Tibbets
Alston & Bird LLP
950 F Street, NW
Washington, DC 20004
Telephone: 202-756-3449

Attachments: Exhibits Nos. 1-30

cc: Gary J. Beuhler, R.Ph., Director, Office of Generic Drugs (without exhibits)
Bob A. Rappaport, M.D., director, Division of Analgesics, Anesthetics and Rheumatology Products (without exhibits)