

**FDA Authority To Require Risk Management Programs
for Generic Versions of OxyContin®**

This memorandum addresses the Food and Drug Administration's authority to require that firms submitting abbreviated new drug applications for controlled-release oxycodone hydrochloride products that list OxyContin® (oxycodone HCl controlled-release) Tablets as the reference listed drug develop and implement appropriate risk management programs ("RMP").

I. Approval of Purdue's December 19, 2003 Supplement Will Provide FDA With Clear Authority to Assure That Generic Applicants Adopt Appropriate RMPs

Upon formal Agency approval of Purdue's December 19, 2003 Changes Being Effected labeling supplement, there will be no question that FDA has the authority to require generic applicants to develop and implement appropriate RMPs.¹ That Supplement advised FDA of changes to the "Warnings" section of the Package Insert for OxyContin that Purdue is implementing immediately. Specifically, the Supplement adds a brief overview of the OxyContin RMP to the Package Insert as follows:

Risk Management Program

The Risk Management Program for OxyContin was developed to assist patients, health care professionals, government agencies and community groups with addressing the proper use of opioid medications, the risk of abusing such products and the concerns of illegal diversion. Such complex issues require a formal risk management program that approaches these

¹ This Supplement, and the other two labeling supplements referenced in the Petition for Stay of Action, arise out of the Agency's consideration of the RMP for Palladone™ at the September 2003 Advisory Committee Meeting and at a December 17, 2003 meeting between Purdue and CDER, as well as the experience with the Accutane® RMP. Indeed, Purdue specifically sought CDER's input on inclusion of references to the Palladone RMP in the Palladone Package Insert, including a paragraph essentially identical to that proposed in Purdue's December 19, 2003 supplement for OxyContin. See December 10, 2003 Letter to Dr. Rappaport, Director, Division of Critical Care and Addiction Drug Products from R. Fanelli, Ph.D., Director, U.S. Regulatory Affairs. Unfortunately, the parties did not have an opportunity to discuss Purdue's proposal during the December 17, 2003 meeting. Because no additional meetings at which the proposal could be discussed were scheduled in the near term, Purdue submitted its OxyContin Supplement two days after that meeting. At the time the Supplement was submitted, Purdue had no way of knowing that the District Court would issue its decision in the Endo patent infringement case on January 5, 2004. Purdue believes that in the future, it may be appropriate for RMPs to be referenced in approved labeling as a routine matter at the time such programs are first adopted as part of the approved conditions of use of a drug product.

KLEINFELD, KAPLAN AND BECKER, LLP

groups and issues from various perspectives. The Risk Management Program for OxyContin presents health care professionals with educational material (printed, electronic, Internet links and formal presentations by experts) on appropriate patient selection, managing pain with opioid products, identifying abuse, and minimizing diversion in their practice; it provides direct intervention in communities through support groups involved with reducing abuse and diversion; it provides assistance to law enforcement through education and materials to assist their activities; and it has established a surveillance program, RADARSM System (Researched Abuse, Diversion, and Addiction-Related Surveillance) that includes a number of ongoing studies that monitor for signs of drug abuse, addiction and diversion of OxyContin that allows for appropriate Company interventions. Further information on any of these activities could be obtained through contacting our 24-Hour Professional Contact Line (1-888-726-7535).

Pursuant to Sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the Act, upon approval of this Supplement, generic applicants will be required to include the same information in the Package Inserts for their products. To ensure that their labeling remains truthful and not misleading under Section 502 of the Act, generic applicants will thus be required to develop and implement RMPs that, at a minimum, have the features referenced in the paragraph.²

In addition, under 21 U.S.C. §355(j)(4)(B), FDA may refuse to approve an ANDA if it finds that the “information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application.” Once Purdue’s December 19th Supplement is approved, Purdue’s RMP may be considered an approved “condition of use” under the NDA within the meaning of Section 505(j)(4)(B) of the Act. As a result, this provision will provide FDA with separate authority to require generic applicants to develop and implement appropriate RMPs, consistent with and supplemental to the approved labeling for the product.

As a necessary corollary, under either provision – Section 505(j)(4)(G) or 505(j)(4)(B) – FDA has authority to refrain from approving ANDAs until the Agency is satisfied that generic applicants’ proposed RMPs address all of the known risks associated with modified-release oxycodone, using properly designed risk management intervention tools that satisfy well-defined risk management objectives consistent with the Purdue RMP.

² The additional two supplements referenced in the Petition for Stay of Action, respectively, (1) propose to insert greater detail regarding the OxyContin RMP into the Package Insert, and (2) seek approval of the entire OxyContin RMP as labeling. Approval of either or both of these supplements would provide additional specific terms which generic firms would be required to adopt verbatim pursuant to §355(j)(4)(G).

II. Section 505(j)(4) of the Act Gives FDA Independent Authority to Refuse to Approve Any ANDA for Modified-Release Oxycodone that is Not Supported by an Adequate Risk Management Plan

While, as discussed above, explicit embodiment of the Purdue RMP into approved labeling pursuant to, for instance, Purdue's December 19, 2003 CBE supplement, would trigger an RMP requirement for the generic products under 21 U.S.C. §355(j)(4)(G), such an approval is not necessary in order for FDA to impose an RMP requirement on OxyContin-based generics. This is because, under 21 U.S.C. §355(j)(4)(B), FDA may refuse to approve an ANDA if it finds that the "information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application." Under a careful analysis of the current status of the OxyContin NDA, this provision should be read as encompassing the OxyContin RMP.³

When OxyContin® was first approved in 1995, there was no expectation of the abuse and misuse of OxyContin® that was subsequently reported.⁴ Accordingly, an RMP was not required as part of the original OxyContin® NDA. However, it is readily apparent that the RMP for OxyContin, as well as the other steps taken by Purdue to address these concerns when they arose, were critical measures in

³ The "conditions of use" terminology in 21 U.S.C. §355(j)(4)(B) could be read to refer simply to indications. See House Report, No. 857, Part I, 98th Cong., 2nd Sess., pp. 21, 25-26. However, the Congress did not use the well-defined term "indications" and instead used the historically more broadly interpreted phrase, "conditions of use." See, e.g., *Food, Drug, and Cosmetic Products, Warning Statements*, Final Rule, 40 Fed. Reg. 8912 (March 3, 1975) ("'conditions of use' [as used in Section 201(n)] is not a narrow term limited to the active handling, operation, and application of a product, but rather includes the entire setting and circumstances in which a product is used"). FDA itself has stated that "conditions of use" as used in section 505(j) of the Act is broader than "indications." See *Abbreviated New Drug Application Regulations*, Proposed Rule, 54 Fed. Reg. 28872, 28881 (July 10, 1989) (proposal to require an ANDA to "include sufficient information to show that the conditions of use, which include, among other things, indications and dosage instructions for which the applicant is seeking approval, have been previously approved for the reference listed drug") (emphasis supplied).

Moreover, §355(j)(4)(B) must be read more broadly than §355(j)(4)(G), which concerns labeling, or it would be superfluous. That is, if the "approved" conditions of use of a product were only those conditions stated in the approved labeling of the product (*i.e.*, the labeled indications), an ANDA that complies with the requirement of §355(j)(4)(G) for identical labeling would, by that fact alone, be assured to embody the same approved "conditions of use." Therefore, in order to have independent meaning, §355(j)(4)(B) must be read as covering "conditions of use" in addition to those specifically stated in the approved Package Insert for the product. We believe that the OxyContin RMP provides a clear example of the types of "conditions of use" that are covered by this separate provision of the law.

⁴ Statement of John K. Jenkins, Director, Office of New Drugs, CDER, FDA, OxyContin: Balancing Risks and Benefits: Hearings Before the Senate Committee on Health, Education, Labor, and Pensions (Feb. 12, 2002) (available at: www.fda.gov/ola/2002/oxycotin0212.html).

KLEINFELD, KAPLAN AND BECKER, LLP

maintaining the positive benefit/risk assessment that has allowed the product to remain on the market in the United States for the past several years. Those critical measures included strengthening the “Warnings,” “Precautions,” and other sections of the OxyContin Package Insert, including the addition of a boxed warning regarding abuse potential and expanded messages to physicians concerning proper patient selection. In addition, Purdue developed a Patient Package Insert that is now part of the approved labeling for OxyContin. Similarly, Purdue distributed a “Dear Health Care Professional” letter to prescribers, pharmacists, and other health care professionals, which describes potential risks associated with OxyContin and explains the changes to the labeling. Purdue also voluntarily ceased distributing the 160-mg tablets due to specific concerns over diversion and abuse of this dosage form.

Finally, in close cooperation with FDA, Purdue developed an enhanced comprehensive RMP to further foster the safe prescribing and use of OxyContin. Specifically, in collaboration with FDA, Purdue developed or supplemented key elements to be included in the RMP, including educational programs for Purdue’s sales representatives, practitioners, and the general public; changes in the product labeling; dissemination of abuse and diversion messages; revision of promotional materials; and formation of alliances with selected professional societies to further the understanding of pain management and addiction. FDA has reviewed and commented on multiple drafts of the RMP since August 2001 and has remained closely involved with components of the RMP. For example, Purdue presented the RMP to the FDA in June 2003 and the FDA provided scientific input to the RADARS® program. The FDA has been invited and has attended the open sessions of the RADARS® External Advisory Board. The RMP resulting from collaboration between Purdue and FDA expands upon the important topics addressed in the currently approved Package Insert – including appropriate use of OxyContin in the treatment of pain, the safe use of OxyContin in appropriate patients, the risks of misuse, abuse, and diversion, and associated concerns such as “drug-seeking behavior” and “doctor shopping” – by implementing specific tools to address these concerns.

As a result of this activity, the “conditions of use” of the product have evolved over time to include the essential safeguards embodied in the OxyContin RMP. Accordingly, at this time, these conditions of use are properly considered part of the OxyContin approval. While, to date, not explicitly the subject of a supplemental approval, the RMP for OxyContin is an inextricable feature of the benefit/risk considerations that underlay the approval of Purdue’s Supplement for a Patient Package Insert on January 15, 2002, and subsequent approvals for changes to the Package Insert, as recently as November 20, 2003. Moreover, inasmuch as Purdue’s response to reports of abuse and misuse of OxyContin made it unnecessary for the Agency to consider proposing to withdraw the NDA approval, the RMP may properly be considered as much a part of the existing approval as the Package Insert.

KLEINFELD, KAPLAN AND BECKER, LLP

For these reasons, we believe that FDA currently has the authority to require generic applicants to develop and implement appropriate RMPs under Section 505(j)(4)(B) of the Act. Again, FDA also necessarily has the authority to refrain from approving ANDAs until it is satisfied that the proposed RMPs are adequate to address the known risks.

Moreover, the failure of generic applicants to develop and implement adequate RMPs comparable to Purdue's would simply authorize FDA to refuse to approve them under 21 U.S.C. §355(j)(4)(G). As FDA has previously explained, the "same labeling" requirement prohibits approval of ANDAs with heightened warnings or precautions intended to address safety concerns not presented by the reference listed drug. In light of the evolving circumstances since OxyContin was first approved, were generic versions of OxyContin marketed at this time without adequate RMPs, at a minimum, it would be necessary to attempt to compensate with significantly enhanced and strengthened labeling concerning misuse, abuse, and diversion, and perhaps a prominent statement disclosing the lack of an adequate RMP. In these circumstances, the ANDA could not be approved:

Thus, where a proposed change in a generic drug . . . would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and 505(j)(3)(G) (sic) of the act.⁵

Accordingly, whether under Section 505(j)(4)(G) or 505(j)(4)(B), FDA currently has the authority to refuse to approve applications for generic versions of OxyContin until those applicants develop and fully implement RMPs that are adequate to address the risks presented by the product.

This view is fully consistent with the Agency's handling of the other situation where there have been ANDAs approved for generic versions of a product that was subject of an RMP – Accutane®. Commenting in Congressional Testimony on the safeguards that would be applied to approvals for generic versions of Accutane, Dr. Woodcock stated:

All generic brands of isotretinoin will utilize the labeling that is alike in all material respects to the name brand, educational tools, distribution requirements, and follow-up metrics in place under S.M.A.R.T. Like the innovator, generic manufacturers are on notice that failure of the risk management plan, or failure to collect valid data, will obligate consideration of more burdensome measures.⁶

⁵ See *Abbreviated New Drug Application Regulations*, Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989).

⁶ Statement by CDER Director, Janet Woodcock, M.D., Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, US House of Representatives (Dec. 11, 2002) (available at: www.fda.gov/ola/2002/accutane1211.html).

As with the Accutane generics, those aspects of the OxyContin RMP which are not yet specifically embodied or directly referenced in the approved labeling for the product are nevertheless properly regarded as approved conditions of use of the product and properly imposed on firms seeking to market generic versions of the product.

III. Case Law is Not Inconsistent with FDA's Authority to Require ANDAs for Modified-Release Oxycodone To Be Supported by Adequate Risk Management Programs

We have considered the potential relevance of *American Pharmaceutical Association v. Weinberger*, 377 F.Supp. 824 (D.D.C. 1974), *aff'd per curiam sub nom.*, *American Pharmaceutical Association v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1976) and *McNeilab, Inc. v. Heckler*, 1985 U.S. Dist. LEXIS 19169 (D.D.C. June 5, 1985) to FDA's authority to refuse to approve ANDAs for generic versions of OxyContin® that are not supported by adequate RMPs. In our view, neither of these cases restricts FDA's authority to refuse to approve such ANDAs.

As an initial matter, neither case interprets Section 505(j) of the Act or in any way addresses FDA's authority to refuse to approve ANDAs that do not include information showing that the approved labeling and conditions of use are the same as the reference listed drug. The Act clearly states that generic drugs must have the same labeling and conditions of use as approved for the reference listed drug, and these cases do not suggest otherwise, much less give FDA authority to ignore these important requirements in Section 505(j). For this reason alone, the cases are inapposite. Moreover, as described below, neither case established broad principles that can reasonably be read to restrict FDA's authority in this matter.

American Pharmaceutical Association v. Weinberger concerned FDA's authority to promulgate regulations restricting distribution of methadone to direct shipments from manufacturers to certain specified outlets, excluding virtually all licensed pharmacies. The Court concluded that once a drug is approved by the FDA, the question of permissible distribution, if it is a controlled substance, is within the jurisdiction of the Justice Department under the Controlled Substances Act.

McNeilab, Inc. v. Heckler involved a challenge to FDA's approval of NDAs for the OTC sale of ibuprofen. The plaintiff alleged that FDA impermissibly conditioned the OTC approvals on commitments about the content of future advertising – a matter within the jurisdiction of the FTC. While the Court opined in dicta that conditioning approval on advertising content would have exceeded FDA's authority, it determined that the record did not support the plaintiff's allegations.

Unlike *American Pharmaceutical Association v. Weinberger*, the instant matter concerns not a regulation, but rather FDA's decisions to approve individual

KLEINFELD, KAPLAN AND BECKER, LLP

applications. Moreover, Purdue's RMP does not involve any restrictions on distribution or any other activity within DEA's sole jurisdiction, and Purdue does not advocate imposition of any such restrictions on generic versions of OxyContin. Rather, the requirements of the OxyContin RMP extend to professional communications and other educational activities squarely within the jurisdiction of the FDA. Relatedly, whether adopted specifically as "labeling," as Purdue has proposed in its pending supplements, or viewed as approved "conditions of use" under §355(j)(4)(B), FDA, not FTC, has jurisdiction over communications about prescription drugs, whether those communications are considered advertising or labeling. Accordingly, neither DEA's nor FTC's authority is implicated by Purdue's Petition for Stay of Action.

The current approved labeling for OxyContin repeatedly emphasizes the appropriate use of OxyContin in the treatment of pain, the safe use of OxyContin in appropriate patients, the risks of misuse, abuse, and diversion, and associated concerns such as "drug-seeking behavior" and "doctor shopping." Purdue's RMP is simply an extension of these aspects of the current approved labeling that implements tools to address the enumerated concerns. Specifically, the RMP further ensures effective communication of the information presented in the currently approved Package Insert, and identifies, through monitoring, those geographical locations where specific interventions may be appropriate to further improve communication of this information. Because Purdue's RMP is essentially, at its core, an extension of the current approved labeling, it falls squarely within FDA's jurisdiction.

Were FDA to conclude that these matters are outside of its authority, it would follow that none of these topics should be referenced in the approved labeling. This is clearly an absurd result, and to the extent that *American Pharmaceutical Association* is read to suggest that all matters related to misuse, abuse, and diversion are outside of FDA's jurisdiction, we believe the case was wrongly decided. In this regard, we note that FDA has had no trouble distinguishing the case in establishing modern approval processes that include distribution restrictions that are closely analogous to the restrictions rejected in the *American Pharmaceutical Association* case.⁷

Underscoring this point, Congress appears to be fully cognizant of FDA's concern with risk management in the approval of drug products and seems to be fully supportive of these, and enhanced, Agency efforts to assure the safe use of drug products approved for marketing in the United States. Thus, after review of FDA's accelerated approval regulations, Congress passed statutory provisions⁸ codifying and

⁷ See 21 C.F.R. § 314.520; *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, Proposed Rule, 57 Fed. Reg. 13234, 13236 (April 15, 1992) and *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, Final Rule, 57 Fed. Reg. 58942, 58951 (Dec. 11, 1992).

⁸ Food and Drug Administration Modernization Act of 1997, Section 112.

KLEINFELD, KAPLAN AND BECKER, LLP

amplifying the provisions of 21 C.F.R. §314.510 (regarding approvals based on surrogate endpoints) but made no changes with respect to the sister provisions at 21 C.F.R. §314.520 – the regulations under which FDA has imposed stringent distribution limitations on several potentially very dangerous drug products, including thalidomide, clozapine, dofetilide, mifepristone, and isotretinoin (Accutane).⁹

Similarly, in its PDUFA III Goals, FDA specifically promised to Congress that, by the end of September 2004, “CDER and CBER will jointly develop final guidance documents that address good risk assessment, risk management, and pharmacovigilance practices.”¹⁰ Far from suggesting a lack of authority to carry through with these important programs, such commitments clearly reflect the shared appreciation by FDA and the Congress of the critical need to assure effective implementation of appropriate risk management and monitoring programs of the sort that have been devised for many drugs over the past several years. In this context, failure to preserve and extend the OxyContin RMP upon approval of generic versions of the product would represent a clear and completely unwarranted abrogation of the Agency’s authority and responsibility to protect the public health.

* * * * *

In summary, we believe that FDA currently has the authority, under either Section 505(j)(4)(G) or 505(j)(4)(B) of the Act, to refrain from approving ANDAs until the Agency is satisfied that generic applicants have developed and implemented appropriate RMPs. This authority will be further strengthened upon formal Agency approval of one or all of Purdue’s labeling supplements referenced in the Petition for Stay of Action.

Respectfully submitted,



Richard S. Morey
Peter R. Mathers
Jennifer A. Davidson
Counsel for Purdue Pharma L.P.

⁹ See Effects on Medical Practice of Regulatory Actions, presentation by Paul J. Seligman, M.D., MPH, CDER (July 16, 2002) (available at www.fda.gov/cder/Offices/OPaSS/WHORegDec1/sld019.htm).

¹⁰ PDUFA Reauthorization Performance Goals and Procedures, Section VIII.e., Enclosure to June 4, 2002 Letter of Tommy Thompson (available at www.fda.gov/oc/pdufa/transltr.html and www.fda.gov/oc/pdufa/PDUFAIIIGoals.html).