THOMAS O. HENTELEFF
RICHARD S. MOREY
KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
ANNE V. MAHER
BONNIE A. BEAVERS
DANIEL R. DWYER
GLENN E. DAVIS
STACY L. EHRLICH
JENNIFER A. DAVIDSON
STACEY L. VALERIO
ROBERT O. WINTERS

OF COUNSEL:
HARVEY A. SUSSMAN
WILLIAM J. HARDY

LAW OFFICES
KLEINFELD, KAPLAN AND BECKER, LLP
1140 NINETEENTH STREET, N.W.
WASHINGTON, D.C. 20036-6606
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
www.kkblaw.com

WEST COAST OFFICE:
ONE MARKET STREET
STEUART TOWER, SUITE 1450
SAN FRANCISCO, CA 94105-1313
TELEPHONE (415) 538-0014
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD
1907-1993

ALAN H. KAPLAN
1930-2001

February 6, 2004

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket # 2004P-0006
Petition for Stay of Action

On behalf of Purdue Pharma L.P. ("Purdue") the undersigned submits this Response to the January 20, 2004 comments filed by Endo Pharmaceuticals ("Endo") on the above-referenced Petition for Stay of Action.[1] Purdue's Petition for Stay of Action requests that the Commissioner of Food and Drugs stay final approval and/or the effective date of final approval of any and all abbreviated new drug applications ("ANDAs") for modified-release oxycodone hydrochloride products that list OxyContin® (oxycodone HCl controlled-release) Tablets as the reference listed drug, unless and until the products covered by those ANDAs are the subject of appropriate risk management programs ("RMPs") consistent with the risk management program for OxyContin. As explained in more detail below, Endo has not shown and, indeed, cannot show that FDA should allow generic versions of OxyContin to be marketed without appropriate RMPs, and therefore Purdue's Petition should be granted.

I. Endo Ignores Commercial Realities That Require Comprehensive Risk Management Programs For Generic Modified-Release Oxycodone Products To Be In Place Prior To Launch

The comments submitted by Endo underscore the critical importance of FDA's swift and positive action on Purdue's Petition for Stay. Those comments state that Endo believes it is fully entitled to begin marketing a generic version of OxyContin without either developing or implementing a RMP tailored to modified-release oxycodone or to the unique issues that marketing a generic version of that drug will present. Endo's proffered commitment to develop and implement some type of RMP at some unspecified time after it

[1] This Response addresses Endo's arguments and is therefore focused on Endo. However, the public policy considerations underlying Purdue's Petition for Stay and this Response apply more broadly to all generic modified-release oxycodone products, as well as any 505(b) applications for modified-release oxycodone products.

begins marketing its generic product alarmingly confirms that Endo fails completely to understand, and is unprepared to meet, the challenges that the marketing of this product will present. In light of the attitude presented by Endo in its comments, it is clear that only FDA can assure that modified-release oxycodone products continue to be marketed in accordance with appropriate RMPs when generic versions of those products are introduced.

The components described by Endo as its current "risk management measures" appear to be little more than a list of legal requirements generally applicable to all controlled drugs. For example, product labeling and distribution chain oversight are required by FDA and DEA regulations. Similarly, Purdue questions whether "proactive surveillance" and "responsive interventions" refer simply to Endo's obligation to review publicly available information and to investigate and report adverse events pursuant to 21 C.F.R. §§ 314.80 and 314.81. While compliance with basic legal requirements is certainly better than violating them, this is hardly what FDA, DEA, and industry have come in recent years to understand as a "risk management program." Characterizing these measures as sufficient to allow approval of Endo's ANDA and launch of Endo's product belies a fundamental misunderstanding of the purposes and content of a properly tailored, comprehensive program directed at reducing the public health risks involved in the marketing of drug products.[2]

Of greatest concern, Endo's proffered justification for relying on its current "risk management measures" instead of developing a comprehensive, tailored RMP for its generic version of OxyContin seems to be based on a fundamental misunderstanding of the conditions under which OxyContin is currently sold and of the potential significance of the entry of generic competitors. First, Endo naively, if not disingenuously, predicts that the entry of generic competitors will reduce the abuse and diversion problem associated with modified-release oxycodone. This prediction is apparently based on the expectation that generic versions of the drug will quickly supplant OxyContin in the marketplace, resulting in curtailed promotional efforts by Purdue – which efforts, according to Endo, have been the primary cause of the abuse and diversion of the drug.

Endo may be correct in predicting that generic modified-release oxycodone products will quickly supplant OxyContin sales. This is a common result following entry of the first generic versions of a branded drug product. The entry of generic versions of OxyContin will also, inevitably, affect Purdue's marketing and promotional activities. However, there is no reason to believe that any abuse and diversion of OxyContin was caused by Purdue's

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[2] We note that Endo recently received an approvable letter for its pending application for a branded extended-release oxymorphone HCl product. Endo has stated FDA requested submission of a RMP and elements of the RMP are under discussion with FDA. In light of this, Endo's assertion that it is appropriate to launch its generic modified-release oxycodone product supported only by limited "risk management measures" and develop a more formal RMP sometime after launch is particularly puzzling.

promotional activities. Just two days after the date of Endo's comments, the United States General Accounting Office issued a report on OxyContin abuse and diversion. The GAO was tasked with determining whether Purdue's marketing may have contributed to abuse and diversion.[3] After a lengthy, thorough investigation, the GAO was unable to conclude that Purdue's promotional activities contributed to abuse and diversion.[4] Similarly, in a Kentucky action in 2001, plaintiffs in *Foister v. Purdue Pharma, L.P.*, Civil Action No. 6:01-268-DCR, tried to obtain an injunction limiting the sale and distribution of OxyContin in the Commonwealth of Kentucky. Plaintiffs asserted that Purdue should be held accountable for an alleged "black-market" for prescription drugs that existed in that state because of what plaintiffs claimed was Purdue's improper marketing and promotion of the medication. After hearing two days of live testimony, the Court categorically rejected Plaintiffs' claims:

> The plaintiffs have failed to produce any evidence showing that the defendants' marketing, promotional, or distribution practices have ever caused even one tablet of OxyContin to be inappropriately prescribed or diverted.

Moreover, there is no indication in the GAO report, and it would be illogical to suggest, that abuse and diversion of modified-release oxycodone products would be curtailed by a reduction in Purdue's promotion of the legitimate use of the drug. To the contrary, the educational efforts of Purdue's sales force, and the extensive sales force training necessary to support those efforts, have been key elements of the OxyContin RMP. Purdue believes that its promotional activities are not the cause of the problem but are, rather, a major part of the solution.[5]

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[3] *Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem*, General Accounting Office, GAO-04-110 (Dec. 2003), published Jan. 22, 2004, at 3 (available at: http://www.gao.gov/) (hereinafter "GAO Report").

[4] GAO Report at 29. While the GAO did not conclude that Purdue's marketing efforts were the cause of abuse and diversion of OxyContin, the GAO did acknowledge that increased availability of modified-release oxycodone in the marketplace may have contributed, along with other factors, to problems with abuse and diversion. GAO Report at 44, 29-32. Of course, as discussed below, marketing of generic versions of OxyContin can be expected to increase availability of modified-release oxycodone.

[5] In this regard, Endo errs in concluding that the public safety will be enhanced by launch of Endo's product because the public will receive the full benefit of Purdue's comprehensive RMP, while at the same time benefiting from the limited "risk management measures" Endo currently employs. Should Purdue's promotional activities slow upon launch of generic versions of OxyContin, as Endo predicts, the benefit of the educational efforts of Purdue's sales force and the extensive sales force training will likewise be reduced. If Endo is unwilling or unable to implement appropriate risk management tools to

In this light, it is ironic that Endo defends its lack of a tailored RMP for generic modified-release oxycodone largely by touting its intention not to use its physician sales force to promote that particular product. Despite the fact that Endo's sales force is regularly engaged in the promotion of Endo's other oxycodone products, namely Percodan® and Percocet®, it apparently intends not to engage those representatives in any educational or other risk management activities with respect to what may well prove to be Endo's largest product ever. According to Endo's January 20, 2004 comments, it does not even intend to train its sales force to answer questions physicians may have about the product while they are in physicians' offices talking about oxycodone. Similarly, although Endo acknowledges that it intends to market its product to retail and wholesale customers, apparently Endo does not intend to employ any risk management tools as part of these promotional activities either.

If Endo is correct that it simply has no responsibility to devise and implement an adequate risk management plan for its generic version of OxyContin, then its comments confirm that the existing RMP for OxyContin will be substantially compromised by the entry of Endo's generic product. Not only does Endo predict that Purdue's efforts will become less effective, it ignores the fact that the total demand for modified-release oxycodone products will likely grow significantly upon the entry of generic competitors.

During the period from 1994 to 2000, for instance, while sales of branded hydrocodone combination analgesic products decreased, sales of generic versions of those products almost tripled and DAWN emergency room mentions for these products doubled. *See* Graph of Hydrocodone Combination Sales and Graph of Hydrocodone Combination DAWN Data, attached hereto as Exhibits A and B, respectively. Thus, the suggestion by Endo that the availability of generic modified-release oxycodone presages a reduction in the abuse and diversion of that drug is unsupported.

Significantly, Endo also ignores the probability that existing prior-authorization requirements imposed by many formularies and third parties on the prescribing and reimbursement for OxyContin will be eased or eliminated upon the availability of generic versions of the drug. Indeed, at least one state's prior-authorization requirement applies only to branded opioids, and this restriction will therefore not apply to generic versions of OxyContin.[6] When these prescribing limitations are lifted, potentially at the active behest of

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address this potential void, risk management efforts may be undermined and progress to date may be reversed.

[6] Mississippi's prior authorization requirement applies only to brand name long-acting oral opioids. In addition, a total of thirty-six other states impose some type of limitation on OxyContin prescribing and/or reimbursement which could be significantly modified or eliminated once generic versions of the product become available. These states are Alabama, Alaska, Arizona, California, Colorado, Delaware,

Endo and other generic competitors, the public is entitled to know: Whose risk management program will be responsible, and effective, for educating and assisting the newly empowered prescribers and their patients to prescribe and use these powerful drugs properly? In devising an appropriate risk management program, taking due responsibility for the inevitable consequences of the marketing of its own products, these are the questions that any marketer of generic modified- release oxycodone needs carefully to consider – yet Endo argues strenuously that it should have no such obligation and openly admits that it is not yet prepared to meet it.

Two days after the date of Endo's comments, the GAO report on OxyContin abuse and diversion confirmed, as its only recommendation, that risk management programs, including measures to monitor use and identify potential abuse and diversion problems, should be adopted for all Schedule II controlled drugs.[7] Both FDA and DEA have heartily concurred in this recommendation. FDA cannot now rationally agree with Endo's suggestion that Endo should be able to commence selling its generic product, armed only with admittedly inadequate risk management measures, and essentially take over the sales of OxyContin.

II. FDA Has The Legal Authority To Impose A RMP Requirement On Endo And Other Generic Applicants And Endo Does Not Deny This Fact

Nowhere in its comments does Endo suggest that FDA would not have the authority to require a RMP for Endo's generic version of OxyContin if FDA were to approve any of Purdue's three pending labeling supplements that pertain to its RMP. Rather, Endo's position appears to be simply that it wants its ANDA approval first, so that it doesn't have to devise and implement an adequate RMP until some undefined time after it has taken over the bulk of the sales of modified-release oxycodone. Indeed, Endo does not even appear to argue that Purdue's RMP labeling supplements should <u>not</u> be approved. Instead, it raises a red herring: that all Purdue would have to do to forestall generic approvals indefinitely would be to submit a revision to its RMP, and related labeling, whenever Endo appeared to be close to having an approvable plan of its own.

Florida, Georgia, Hawaii, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, Tennessee, Utah, Vermont, Washington, West Virginia, and Wyoming. Limitations imposed in these states include prior authorization requirements for all OxyContin prescriptions, limitations on the number of tablets per prescription or per month, limitations on the number of milligrams prescribed per day, and requirements that physicians must first attempt to achieve adequate pain control with other drugs, among others.

[7] GAO Report at 42.

The fallacy in Endo's argument, of course, is that Purdue has no control over whether or when FDA approves revised labeling for its OxyContin product, just as Purdue has no control over how FDA chooses to respond to its Petition for Stay. If FDA concurs that the current RMP for OxyContin should be reflected in the product's approved Package Insert, it can and should approve a revised insert. FDA can, for instance, approve the general references to Purdue's RMP as proposed in Purdue's December 19, 2003 CBE supplement. If FDA concurs that it would also be appropriate for the approved labeling for the product to include additional detail about the RMP, FDA can approve Purdue's second pending CBE supplement. If FDA agrees that the entire RMP for OxyContin should be approved as labeling, it can approve Purdue's third pending supplement. If FDA takes one or more of those actions, and Purdue were to submit further labeling supplements pertaining to its RMP at a later time, FDA could either approve or reject those changes as well, as the Agency deems appropriate. When Endo, or any other would-be manufacturer of generic modified-release oxycodone has a RMP ready that is consistent with the approved labeling for the listed drug and that is otherwise acceptable to FDA, FDA can approve those generic products. [8]

This is exactly the approach that FDA took with generic versions of Accutane®. In its decision on Hoffmann-LaRoche's Accutane petition, which Endo does not appear to criticize, FDA announced that it would require generic applicants – prior to launch – to duplicate every aspect of both the Accutane labeling and the Accutane RMP, including the Roche educational programs, prescription validation programs, and program effectiveness measurement procedures and tools. Although FDA recognized that there could be some variations in the precise details of the various manufacturers' plans and language, it did not allow any manufacturer to rely on the program or materials of another manufacturer to meet its own RMP obligations. Indeed, FDA acknowledged that there was duplication involved in the RMP requirements as imposed on the generic manufacturers but, FDA concluded, that was what was legally required once the RMP is reflected in the labeling of the listed drug.[9] This is no more than Purdue asks FDA to require of manufacturers of generic versions of

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[8] Endo raises another red herring when it complains that it would be inappropriate for FDA to require duplication of confidential portions of a RMP. In fact, Purdue has never urged FDA to require any more of generic applicants than is described in Purdue's three labeling supplements, all of which have been submitted to this Docket and are publicly available. If additional measures are to be required of Endo, this would be because FDA determines that the marketing of generic versions of OxyContin raises different or additional concerns than does the marketing of OxyContin itself.

[9] *See* Letter from J. Woodcock to E. Flannery (Nov. 8, 2002), Docket 02P-0059 (available at: http://www.fda.gov/ohrms/dockets/dailys/02/Nov02/111502/02p-0059-pav0001-vol1.pdf). In light of FDA's decision, Endo's selected quotes from and attempts to rely on that letter decision (Endo Comments, pp. 11-12, 16) are simply misplaced.

OxyContin. Indeed, the only aspect of the Roche petition that FDA rejected was Roche's suggestion that the RMP be read to preclude substitution of the generic products for prescriptions that referenced the Roche program. Purdue has not suggested any such reading of the OxyContin program, or that FDA should in any other way prevent substitution of approved AB-rated generic versions of OxyContin.

III. Purdue Submitted Its Petition In A Timely Manner, To Coincide With The First Occasion FDA Would Have To Consider These Questions, While Endo Should Not Have Been Surprised By The Need For A RMP Before Launching Its Generic Version Of OxyContin

Given the extensive press coverage and extensive public consideration and educational efforts by FDA and DEA regarding both the abuse and diversion of OxyContin and the OxyContin RMP, Endo is in no position to complain that it was surprised that FDA would consider the need for a RMP in connection with the review and final approval of Endo's ANDA. Endo's comments indicate, however, that it has been seeking approval to market generic modified-release oxycodone without making any efforts to develop a RMP appropriate for that product. Endo provides no rational explanation for its delay or its position that a RMP should be put in place only after Endo launches its generic product. While it may have been perfectly understandable for Endo to have deferred consideration of necessary RMP design and preparation during the pendency of patent litigation, Endo's choice in this regard hardly creates a valid basis to defer the necessary planning and implementation of an appropriate RMP until after Endo commercially releases its generic product.[10]

On the other hand, Purdue's three labeling supplements, and its Petition for Stay, arise out of the Agency's recent consideration of Purdue's RMPs for OxyContin and Palladone™ (hydromorphone HCl extended-release) Capsules, as well as the experience with the Accutane RMP.[11] While the OxyContin RMP has been implemented for several years,

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[10] Endo's suggestion that it should be able to launch without a RMP because, years ago, Purdue launched without a RMP is astounding. As Endo elsewhere acknowledges, and as FDA has publicly stated, when OxyContin was first approved in 1995, there was no expectation of the unusual abuse and misuse of OxyContin that was subsequently reported. *See* 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/oxycontin0212.html). Now that conditions have changed, public health considerations preclude approval of generic modified-release oxycodone products with nonexistent, insufficient, or inconsistent RMPs that fail to adequately address the risks that accompany these drug products or impede the effectiveness of the RMP for OxyContin.

[11] Palladone is Purdue's hydromorphone hydrochloride extended-release capsule product, which is the subject of NDA # 21-044, currently pending before the Agency.

features of it – particularly those also incorporated into the proposed Palladone RMP – have been the subject of ongoing discussions with FDA including a meeting between Purdue and CDER in the summer of 2003 and an Advisory Committee meeting in September 2003.[12] Indeed, in early December 2003, 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. Although the parties did not have an opportunity to discuss Purdue's specific proposal during their December 17, 2003 meeting, based on an exchange at that meeting about the Agency's position on RMPs for single-entity modified-release opioids, Purdue submitted a CBE labeling supplement to the OxyContin NDA two days later, on December 19, 2003. All of these activities were undertaken at a time when Purdue reasonably believed that generic versions of OxyContin (and Palladone) could not legally be marketed for many years.[13] Upon issuance of the unexpected decision of the District Court in the Endo patent infringement case on January 5, 2004, however, there was, for the first time, a real possibility that generic versions of the drug could be approved in the near future and, concomitantly, a need for careful and expedited consideration of the manner in which such drugs would be commercially introduced – and the effect of that entry if they were not the subject of appropriate RMPs. In order to alert and assist FDA in considering these matters, Purdue filed its Petition as quickly as possible and also submitted the additional labeling

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[12] Endo misleadingly suggests that comments at the Advisory Committee meeting indicate that FDA is unsatisfied with Purdue's RMP and hints that the Agency may require changes to the RMP. In fact, Dr. Sharon Hertz stated that "While I am going to be reviewing what we think might be some of the limitations for this plan, I just also want to state that we should keep in mind that this represents one of the most detailed plans that has been established so far [for modified-release opioids] and it really represents I think one of the best efforts so far." *See* Transcript of Anesthetic and Life Support Drugs Advisory Committee Meeting (Sept. 10, 2003), pp. 180-81, 336 (available at: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3978T2.PDF).

[13] Purdue had every reason to believe that it would succeed on its claims for patent infringement against Endo. Indeed, the Court had previously granted, and the Federal Circuit affirmed, Purdue's motion for preliminary injunctive relief in the *Roxane* action, finding that Purdue was likely to prevail on its infringement claims and that Roxane's defenses of invalidity and unenforceability lacked substantial merit. *See Purdue Pharma L.P. et al v. Boehringer Ingelheim GmbH, et al,* 98 F.Supp.2d 362 (S.D.N.Y. 2000), *aff'd*, 237 F.3d 1359 (Fed. Cir. 2001). Thus, given the prior decisions, Purdue had every reason to believe it would be just as successful against Endo and other generic applicants as it was against Roxane.

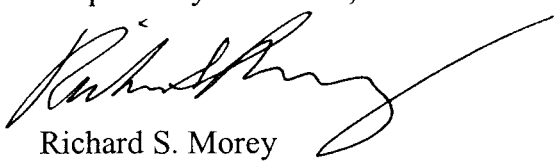
Indeed, based on Purdue's conviction that the January 5, 2004 Court decision was wrongly decided, it is currently seeking a stay of that decision and an extension of the stay of approvals in both the Endo and Teva patent litigations. Purdue's appeal of the January 5, 2004 Court decision was docketed in the Federal Circuit on February 2, 2004, and Purdue intends to move for an expedited hearing on its appeal early next week. In this regard, Purdue is not alone in its concern that the January 5, 2004 decision not stand as precedent. A past commissioner of the Patent and Trademark Office has already published an article criticizing the January 5 decision and advocating its reversal on appeal. *See* Bruce A. Lehman, *The OxyContin Case - A Decision Unlikely to Stand*, 2 Patents (BNA) 130 (Jan. 30, 2004).

supplements that FDA may find helpful in ensuring that generic oxycodone products are not approved for marketing without first being the subject of adequate and appropriate RMPs devised and implemented by their respective manufacturers. In light of this timeline, Endo's repeated suggestion that Purdue's Petition for Stay should be disregarded as simply a delay tactic must be rejected.

IV. Conclusion

Purdue's Petition for Stay established the significant public health benefits of ensuring that the risk management controls for all modified-release oxycodone products are consistent over time. The Petition also highlighted the potential dangers of permitting generic versions of OxyContin to be marketed with nonexistent, insufficient, or inconsistent RMPs that fail to adequately address the risks that accompany these drug products or impede the effectiveness of the existing RMP for OxyContin. Endo's refusal to proactively consider commercial realities and the corresponding unique issues that marketing a generic version of OxyContin will present, or to voluntarily tailor its existing "risk management measures" specifically to modified-release oxycodone, underscores the need for FDA intervention to ensure that generic applicants develop and implement appropriate RMPs prior to FDA approval of their ANDAs. Accordingly, Purdue urges the Agency to grant its Petition and stay final approval and/or the effective date of final approval of any and all ANDAs for modified-release oxycodone products, unless and until the products covered by those ANDAs are the subject of appropriate RMPs consistent with the RMP for OxyContin.

Respectfully submitted,



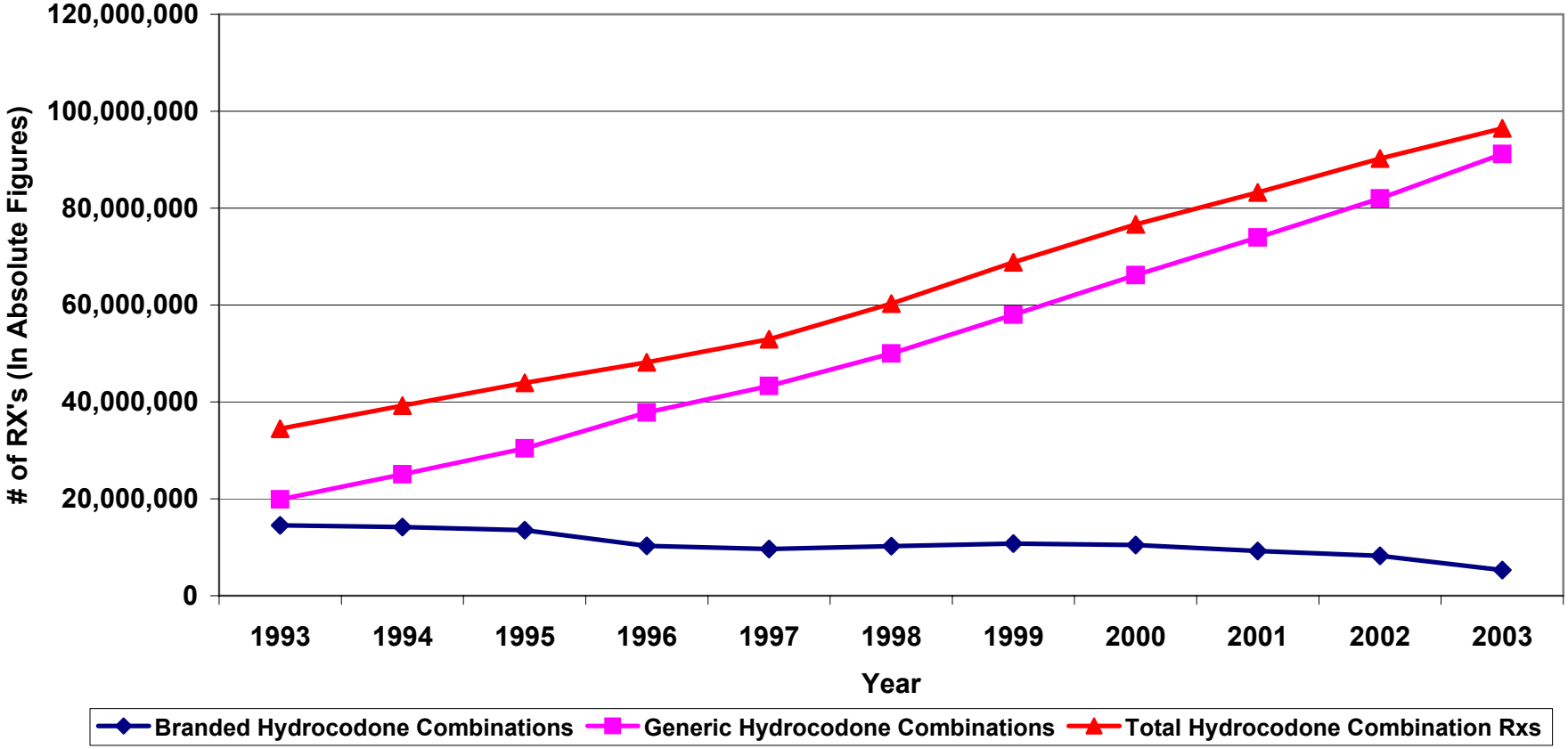
Richard S. Morey
Peter R. Mathers
Jennifer A. Davidson
Counsel for Purdue Pharma L.P.

Exhibit A

Annual Prescriptions for Hydrocodone Combination Products* - 1993-2003

(Prescriptions filled in Retail Pharmacies, Long-Term Care and Mail Order)

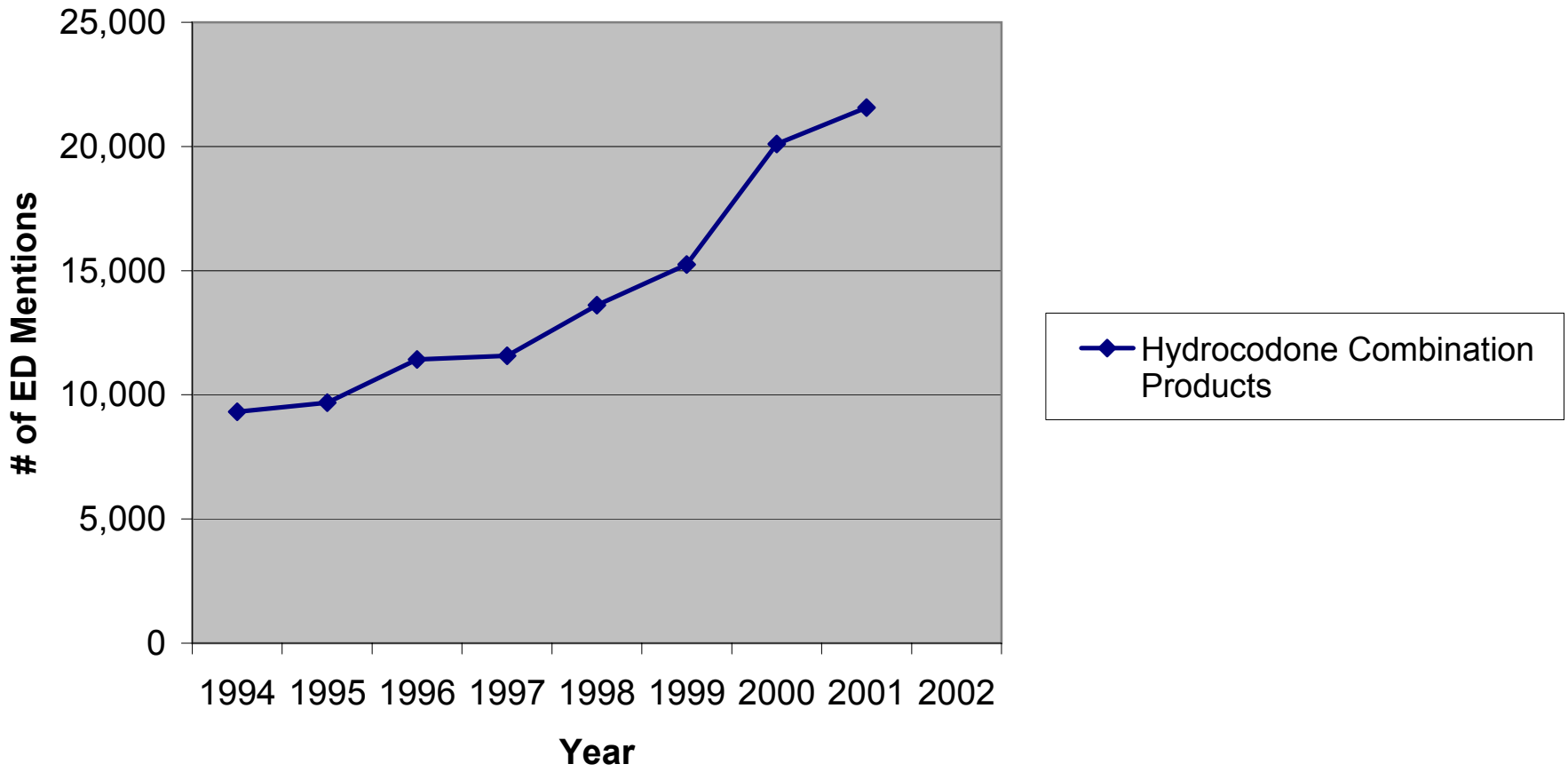
Source: IMS HEALTH's *National Prescription Audit™ (NPA)*



*Excludes Cough and Cold Formulations

Exhibit B

Figure 1: # of ED Mentions for Hydrocodone Combination Products*, Drug Abuse Warning Network (DAWN): 1994-2001



* Excludes Cough and Cold Formulations