

LAW OFFICES  
**KLEINFELD, KAPLAN AND BECKER**

1140 NINETEENTH STREET, N.W.

WASHINGTON, D. C. 20036-6601

TELEPHONE (202) 223-5120

FACSIMILE (202) 223-5619

E-MAIL: kkb@kkblaw.com

2505 '99 MAY 18 P2:44

May 18, 1999

ALAN H. KAPLAN  
THOMAS O. HENTELEFF  
RICHARD S. MOREY  
PETER O. SAFIR  
KINSEY S. REAGAN  
PETER R. MATHERS  
WILLIAM J. HARDY  
BONNIE A. BEAVERS  
DANIEL R. DWYER  
GLENN E. DAVIS  
PRESCOTT M. LASSMAN  
STACY L. EHRLICH

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

E. U. COUNSEL  
SQUIRE, SANDERS & DEMPSEY  
BRUSSELS, BELGIUM  
011 3 226 271 111

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

9834 15 MAY 21 P4:13

**Citizen Petition**

Dear Sir/Madam:

The undersigned respectfully submit this petition under Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA") and Section 10.25 of FDA's regulations on behalf of Purdue Pharma L.P. ("Purdue"), holder of approved New Drug Application 20-553 for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets, 10 mg, 20 mg, 40 mg, and 80 mg. ("OxyContin®").

**A. Action Requested**

This petition requests that New Drug Application 20-932 covering Roxicodone™ (oxycodone HCl) Sustained Release Tablets, 10 mg and 30 mg ("Roxicodone™"), submitted and held by Roxane Laboratories, Inc. ("Roxane") (together with any pending supplements or amendments dependent upon that application for other dosage strengths of extended release oxycodone HCl tablets) be recognized as an application covered by §505(b)(2) of the FFDCA and that the purported October 26, 1998 effective approval of that application under §505(b)(1) be declared by FDA to be null and void as having been issued in violation of FDA's statutory authority and Purdue's rights under the 1984 Amendments to the FFDCA.

Petitioner also requests that any future approval of a Roxane NDA for a sustained release oxycodone tablet preparation be issued by FDA only after Roxane complies with all statutory and regulatory standards applicable to §505(b) applications including, if a

99P-1589

CPI

§505(b)(2) application, appropriate certifications with respect to patents covering Purdue's OxyContin® Controlled Release Tablets.

**B. Statement of Grounds**

Roxicodone™ (oxycodone HCl) SR Tablets, 10 mg and 30 mg strengths, were approved by FDA on October 26, 1998 under NDA 20-932 submitted by Roxane. Those approvals followed, by less than three years, the approvals of Purdue's NDA 20-553 for OxyContin® (oxycodone HCl) CR Tablets, 10, 20 and 40 mg strengths on December 12, 1995 and an additional 80 mg strength on January 6, 1997. The Summary Basis of Approval documents ("SBA") for the Roxicodone™ application, released by the FDA under the Freedom of Information Act on December 22, 1998, demonstrate that the Roxicodone™ NDA should have been classified and processed by FDA as a §505(b)(2) application. Because it was not, it appears that there were significant legal deficiencies in the processing of that NDA, as demonstrated and discussed below.

In light of these legal deficiencies, the October 26, 1998 purported effective approval of the Roxicodone™ NDA exceeded FDA's statutory authority and is null and void.

**1. The Roxicodone™ NDA was processed as a §505(b)(1) application but was, in fact, a §505(b)(2) application.**

In 1984, Congress amended the new drug provisions of the FDCA to provide specific procedures for review and approval of applications for drug products which rely (in whole or in part) on another party's data to establish safety and effectiveness. Under those procedures, the submission and/or effective approval of such applications are potentially subject to "exclusivity" delays and, where patents are listed as covering previously approved products, the applicant for new products must make certain certifications regarding those patents. Those procedures and limitations apply whenever an application is submitted in "abbreviated" form under §505(j), or in the form of a §505(b)(2) NDA "for which the [full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted". (FDCA, §505(b)(2))

a. **Reliance on Non-Roxane Data to Establish the Safety and Effectiveness of the Roxane Products**

A review of the Roxicodone™ SBA indicates that Roxane conducted a number of studies of its own. However, the SBA also makes clear that both Roxane and FDA relied, in approving the NDA, on data from studies of oxycodone that were not conducted by or for Roxane. Moreover, the SBA does not indicate that Roxane possessed a right of reference to any of those non-Roxane studies. Reliance on any safety or effectiveness studies that were not conducted by or for Roxane, and to which Roxane did not possess a right of reference, subjects the Roxane application to the restrictions of §505(b)(2) status.

(1) The design of the Roxane clinical studies itself reflects Roxane's reliance on prior data and experience with oxycodone. Instead of placebo, the Roxane studies used an immediate release formulation of oxycodone as an "active" control.<sup>1</sup> This study design requires reliance on the conclusion that oxycodone had already been shown (in studies of approved single entity drug products) to be safe and effective. However, there is no indication that Roxane had either conducted or obtained a right of reference to all of the clinical and preclinical studies necessary to establish the safety and effectiveness of oxycodone as a chemical entity. Rather, from the SBA, Roxane appears to have submitted and relied upon dozens of published studies including "48 published articles relating to the clinical pharmacology, efficacy and safety of the drug substance, oxycodone," without any indication that it had a right of reference to any of the studies or data reported in those articles. (CDER, Review and Evaluation of Clinical Data, NDA 20-932, page 8.)

(2) One of the published articles submitted by Roxane and referenced in the SBA is a report of a study by Sunshine, et al., entitled "Analgesic Efficacy of Controlled-Release Oxycodone in Postoperative Pain," J. Clin. Pharmacol. 1996:36:595-603. (See CDER, Review and Evaluation of Clinical Data, NDA 20-932, page 11, reference 7.) This is the published report of Purdue's Study 88-1105, one of the two placebo controlled clinical studies of OxyContin® included in OxyContin® NDA 20-553. Purdue has not granted Roxane a right of reference to this study or any of the other pivotal OxyContin® studies. Yet this is the only report of a placebo controlled study of extended release oxycodone submitted by Roxane. This is significant because none of the "pivotal" clinical studies actually

---

<sup>1</sup> The SBA also includes a comment by an agency reviewer that the immediate release oxycodone active control utilized by Roxane was an "approved" drug. (CDER Statistical Review and Evaluation, NDA 20-932, page 19.) This comment is incorrect – immediate release oxycodone is not and has never been approved by FDA as a single entity drug product. Moreover, reliance on the safety and effectiveness of a precursor product, whether approved or not, triggers §505(b)(2) status for an NDA unless the applicant also happens to own or have an explicit right of reference to the data necessary to establish the safety and effectiveness of that precursor product.

conducted and submitted by Roxane (which used only “active” controls) appears to have met standard statistical criteria for establishing the effectiveness of drugs. That is, they showed neither statistical superiority over the active treatment control nor statistical equivalence to the control. (CDER, Statistical Review and Evaluation, NDA 20-932, pages 18-22.) No consideration was apparently given by the FDA reviewers to how Roxane’s data, on its own, could meet the substantial evidence requirements of the FDCA. The presence of the Purdue data, however, which did provide statistical proof of the effectiveness of extended release oxycodone tablets, and the prior approval of Purdue’s product, therefore appears to have been a critical factor in the approval of the Roxane NDA.

(3) Purdue was expressly required by FDA to conduct toxicology studies of oxycodone for inclusion in its OxyContin® NDA, specifically new Segment II teratology studies involving rats and rabbits, as a precondition to the approval of OxyContin®. (See Exhibit 1, Declaration of Joseph Tigner, and Exhibit 2, Purdue draft Meeting Minutes, June 23, 1993, page 7<sup>2</sup>). Roxane was apparently not required to conduct any such studies. Instead, the Roxane SBA refers expressly to the prior review of the Purdue application in the context of not requiring further toxicology data from Roxane:

“Oxycodone was recently reviewed in [Purdue’s OxyContin®] NDA 20-553 and no new non-clinical data of significance has been found or submitted.”  
(Review and Evaluation of Pharmacology/Toxicology Data, NDA 20-932, page 2.)

“Animal carcinogenicity and reproduction studies” were specifically identified by FDA as one of the several types of studies sponsors of new drug applications would be required to duplicate if they wished to avoid §505(b)(2) status and thereby to circumvent prior applicants’ rights to non-patent exclusivity and patent certification. (See Abbreviated New Drug Applications, Proposed Rule, 54 Fed. Reg. 28872, 28891, July 10, 1989.) Even if the SBA had not mentioned the OxyContin® NDA in this context, the failure of FDA to require Roxane to duplicate the Segment II teratology studies it had just a few years earlier expressly and unambiguously required of Purdue would be a fatal flaw in its consideration and approval of the Roxane application. The fact that the OxyContin® review was explicitly referenced, however, dramatically reinforces the conclusion that the Roxane NDA was a §505(b)(2) application that relied, at least in part, on Purdue data to which Roxane had absolutely no right to refer.

---

<sup>2</sup> The Purdue draft minutes of its June 23, 1993 meetings with CDER, excerpted in Exhibit 2, were submitted to FDA as part of the OxyContin® IND on August 5, 1993. Purdue did not prepare any minutes of those meetings which were designated as “final” and does not have any FDA-prepared draft or final minutes of the meetings.

(4) We have also identified further references in the SBA to prior clinical data relied on by Roxane and FDA in support of the safety of Roxicodone™. In the Review and Evaluation of Clinical Data for NDA 20-932, there appears the following discussion of safety data pertaining to the use of extended release oxycodone in patients with renal impairment:

“Only 3 of the 126 patients who received oxycodone SR and 3 of the 126 patients who received oxycodone IR in the controlled clinical studies were considered renal-impaired . . . . This sample was too small for comparisons to be made. In studies conducted previously in patients with renal impairment, as evidenced by decreased creatinine clearance . . . , the concentrations of oxycodone in the plasma are higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.”

(CDER, Review and Evaluation of Clinical Data, NDA 20-932, page 78.) The reference to “studies conducted previously” would encompass Purdue’s unpublished clinical studies in patients with renal-impairment as well as a study by Kirvela, et al., “The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation.” *J. Clin. Anesth.*, 8(1); 13-18 (1996), cited in the Roxicodone™ SBA (CDER, Clinical Pharmacology and Biopharmaceutics Review, NDA 20-932, page 14). There is no indication whatsoever that Roxane has a right of reference to either of these studies.

The FDA evaluations of data pertaining to the use of oxycodone in patients with hepatic failure similarly note that Roxane’s attempts to “tease out” data on this issue from its own studies were unsuccessful. (See CDER, Clinical Pharmacology and Biopharmaceutics Review, NDA 20-932, page 14.) As was the case with Roxane’s “missing” data on renal impairment, however, the reviewer was able to evaluate whether use in hepatic failure populations was a problem:

“In studies conducted previously in patients with hepatic impairment, the plasma concentrations of oxycodone are greater than those in patients with normal liver function. The initiation of therapy at 1/3 to 1/2 of the usual doses and careful titration is warranted.” (CDER, Review and Evaluation of Clinical Data, NDA 20-932, page 78.)

To the best of our knowledge, the only studies of the type described in this review were conducted by Purdue and included in the OxyContin® NDA. Purdue has not provided Roxane with a right of reference to those studies. (Exhibit 3, a Declaration of Robert F. Reder, explains how FDA required, as a condition of approval, that Purdue conduct clinical studies in patient populations with renal impairment and hepatic impairment. See also the draft Meeting Minutes at Exhibit 2, page 13.)

The above examples clearly demonstrate that Roxane's application is a §505(b)(2) application – an application that 1) relies on active treatment controls that are assumed to be effective based solely on historical data; 2) does not include statistically significant evidence from the sponsor that its product was even as effective as the unapproved active controls it used in its studies; but 3) explicitly cites data from the prior sponsor which provides statistically significant evidence of effectiveness of extended release oxycodone. The fact that the FDA toxicology reviewer actually cited the Purdue application in discussing crucial additional data that Roxane had not included in its application (data which had been regarded as essential to the approval of Purdue's application just a few years earlier) provides further undeniable proof that the Roxane application was covered by §505(b)(2) and subject to Purdue's statutory rights to non-patent exclusivity and patent certification. The similar references by the clinical reviewer to "studies conducted previously in patients with renal impairment . . . [and] hepatic impairment . . ." also underscore the extent to which the review and approval of the Roxane application was improperly intertwined with the agency's awareness of important study data which FDA required Purdue to generate and include in the OxyContin® NDA.

Significantly, given the obvious importance of assuring that §505(b)(2) applications are subjected to the applicable restrictions and public health safeguards, the Roxicodone™ SBA is completely devoid of evidence that the agency even considered whether the Roxane application could stand entirely on Roxane data and data to which Roxane had a right of reference. Rather, it appears that the reviewers simply never addressed the question of whether the application was covered by §505(b)(2). This sharply contrasts with the attention this issue has received by FDA in the past – most notably in the preambles to the NDA/ANDA regulations, as outlined in the following discussion.

**b. As a Consequence of Roxane's Reliance on Other Parties' Data, The Roxicodone™ NDA Was Covered By Section 505(b)(2)**

On the facts outlined above, there should be no question that the Roxicodone™ application was (and continues to be) covered by §505(b)(2) of the FFDCFA. The following statements by FDA in the preambles to the regulations implementing the 1984 Hatch-Waxman Amendments confirm this conclusion:

"Thus, section 505(b)(2) of the act is not restricted to literature-supported NDA's for duplicates of approved drugs; it covers all NDA's for drug products that rely on studies not conducted by or for the applicant or for which the applicant does not have a right of reference." (Patent and Exclusivity Provisions, Final Rule, 57 Fed. Reg 17950 at 17952, April 28, 1992.)

“Accordingly, an application is described by section 505(b)(2) of the act if the applicant has not conducted or sponsored or obtained a right of reference to every safety or effectiveness investigation without which the drug could not be approved. An application that contains one study conducted by the applicant but that relies on literature citations for the remainder of the safety and effectiveness data without rights of reference is thus considered an application described by section 505(b)(2) of the act.” (Abbreviated New Drug Applications, Proposed Rule, 54 Fed. Reg. 28872, 28891, July 10, 1989.)

“In addition to applications supported by literature reports or a combination of literature reports and new clinical investigations, FDA is proposing to treat as a 505(b)(2) application an application for a change in an already approved drug supported by a combination of literature or new clinical investigations and the agency’s finding that a previously approved drug is safe and effective.” (Id.)

“FDA . . . believes that it would be inconsistent with the policies of the 1984 Amendments to allow these applications to rely on the approval of a listed drug unless they were subject to the listed drug applicant’s patent rights and exclusivity. Therefore, an application that relies in part on the approval of a listed drug is, for this purpose, considered an application described in section 505(b)(2) and must make a certification as to any relevant patents that claim the listed drug. In addition, the date of submission and effective approval of these applications may, under section 505(c)(3), be delayed to give effect to any patent or period of exclusivity accorded the listed drug.” (54 Fed. Reg. at 28892-3.)<sup>2</sup>

Similarly, persons seeking to avoid §505(b)(2) classification are faced with a very high burden that Roxane apparently made no attempt to meet (and the FDA reviewers apparently failed to apply):

**“In light of this interpretation, an applicant seeking to submit a so-called ‘full NDA’ and thereby avoid any exclusivity or patent rights attaching to a pioneer drug must conduct or sponsor the adequate and well-controlled investigations necessary to establish the effectiveness of the drug, or, if the applicant relies on literature for these studies, must obtain rights of reference to the data. The applicant must conduct, sponsor, or obtain**

---

<sup>2</sup> Application of these standards logically follows, as FDA has recognized, even when the applicant makes no explicit reference to the drug it appears to duplicate. See 54 Fed. Reg. 28897.

rights of reference to these studies even if the pioneer applicant relied on literature citations. Similarly, the applicant must conduct, sponsor, or obtain a right of reference to all the safety tests without which the application could not be approved. In general, such tests will include animal carcinogenicity and reproduction studies, certain animal toxicity studies and some clinical investigations. When a drug product has a U.S. marketing history, an analysis of the spontaneous adverse reaction reports may, in some cases, be substituted for some of the safety data described.” (Id. at 28891.)<sup>3</sup>

“This interpretation is consistent with Congress’ intent to encourage the pharmaceutical industry to develop and seek approval of significant new therapies by conferring periods of exclusive marketing. If exclusivity could easily be avoided by an application containing only minimal data generated or purchased by the applicant, the incentive created by the availability of such exclusivity would decrease considerably.” (54 Fed. Reg. at 28891.)

Indeed, in the context of these considerations, FDA explicitly decided that NDAs which rely on prior “DESI-effective” determinations (a situation analogous to the reliance on the purported “general recognition of safety and effectiveness” of a drug substance) must be considered 505(b)(2) applications:

“An applicant seeking approval of a drug product covered by a DESI upgrade notice before a product is approved for safety and effectiveness under that notice should submit a 505(b)(2) application to the Office of Generic Drugs. Generally the 505(b)(2) application must contain the information specified in section 505(b)(2) of the act, except that the labeling must meet the conditions of use announced as effective in the relevant DESI upgrade notice. In satisfying the full reports of investigations requirement under section 505(b)(1)(A) of the act, the applicant may refer to the agency’s conclusions in the DESI upgrade notice about the product’s safety and effectiveness and must demonstrate that the proposed drug product is bioequivalent to the drug product that is the subject of the relevant DESI upgrade notice. The agency will generally employ the same mechanisms and standards in approving a

---

<sup>3</sup> FDA made clear in response to comments on this statement that an analysis of marketing history and of spontaneous ADR reports would not be expected to substitute for all of the safety information required in connection with a “full” NDA approval. (See 57 Fed. Reg. 17954, paragraph 7, April 28, 1992.)

section 505(b)(2) application for a DESI drug that it would for an ANDA under section 505(j).” (57 Fed. Reg. at 17963.)

2. **As a Result of the Failure to Process the Roxicodone™ Application Under Section 505(b)(2), the Roxicodone™ NDA Approval Was Illegally Issued and Purdue’s Statutory Rights Were Violated**
  - a. **Approval of the Roxicodone™ Application on October 26, 1998 Was Legally Precluded By Purdue’s FDA-Acknowledged Non-Patent Exclusivity Rights**

FDA’s purported “effective approval” of the Roxicodone™ application on October 26, 1998, was not legally valid. October 26, 1998 was approximately two months prior to the expiration of the three-year “new-dosage-form” non-patent exclusivity under FFDC §505(c)(3)(D)(iii) which attached to Purdue’s OxyContin® approvals of December 12, 1995. As a §505(b)(2) application for the same dosage form as OxyContin® (i.e., extended release tablets), neither strength of Roxicodone™ should have been approved before December 12, 1998 at the earliest. This is doubly so in the case of the 10 mg Roxicodone™ product, which duplicates not only the extended release tablet dosage form but also the labeled strength of one of the approved OxyContin® products – each of which was separately entitled to exclusivity through December 12, 1998.

Given that FDA lacked the legal authority to approve the §505(b)(2) Roxicodone™ application on October 26, 1998 by virtue of the limitation imposed by §505(c)(3)(D)(iii), that approval is null and void and of no effect. It has been FDA’s consistent policy that a “prospective” or “tentative” approval of an NDA affected by exclusivity delays is not an approval and does not become an effective approval “automatically” by virtue of the expiration of the applicable exclusivity. Rather, after expiration of applicable exclusivity periods, official NDA approval requires the issuance of a separate effective approval letter. (See 21 C.F.R. §314.107(b)(3)(v); CDER MAPP 4520.1) Therefore, unless and until FDA issues a new, valid approval of the Roxicodone™ application, Roxane has no effective legal authority to market its Roxicodone™ products and should be so informed formally by the agency so that there is no ambiguity in that regard.<sup>4</sup>

---

<sup>4</sup> Such action would not even require FDA to invoke its inherent authority to “revoke” an approval issued by “mistake.” For example, in *American Therapeutics, Inc. v. Sullivan*, 755 F. Supp. 1 (D.D.C. 1990), the Court upheld FDA’s revocation of an approval granted to American Therapeutics that, while legally issued by the agency, was later determined to have been issued during a GMP investigation that had uncovered facts that would have justified delaying an approval decision. The circumstances of FDA’s approval of Roxane’s application would certainly qualify for

As explained below, however, issuance of an effective approval of the Roxicodone™ application must await compliance by Roxane with the additional significant legal prerequisites to the approval of a §505(b)(2) application which continue in effect beyond the expiration of non-patent exclusivity.

**b. FDA Should Have Refused To File The Roxane Application For 10 mg Controlled Release Oxycodone Tablets Because That Product Was Eligible For ANDA Approval (Though Not “Effective Approval”)**

If the Roxicodone™ application had been properly presented by Roxane and recognized by FDA as a §505(b)(2) application, FDA should nevertheless have refused to file the application with respect to the 10 mg strength. This is because, under 21 C.F.R. §314.101(d)(9), FDA may refuse to file an application that “is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval<sup>5</sup> under section 505(j) of the act.” The Roxicodone™ 10 mg tablets are a duplicate of OxyContin® 10 mg tablets (i.e., same dosage form, dosage strength, and route of administration) and should have been required by FDA to be submitted either in an ANDA under §505(j) or in a §505(b)(1) full NDA.<sup>6</sup>

The reason for this requirement is precisely to avoid what has happened with the approval of the 10 mg Roxane product – FDA has now approved for marketing two officially non-substitutable versions of the same drug. As explained in the following section, Congress and FDA have both clearly expressed the view that a duplicate of a previously approved drug should be bioequivalent to the pioneer product. Otherwise, confusion over the differences in therapeutic effects between pioneer and generic versions of the same drug could lead to inadvertent dosing errors and potentially serious problems. In addition, widespread availability of nonequivalent generic drugs would have the effect of undermining confidence in the market for generic drugs -- a confidence that is based in large part on FDA enforcement of proper standards of bioequivalence. In the case of §505(b)(1) applications that are not also covered by §505(b)(2), there may be nothing FDA can do to prevent this.

---

similar treatment. More importantly here, the approval of Roxane’s application was not simply a policy oversight; it was also legally impermissible. Thus, FDA need not even invoke the authority recognized in *American Therapeutics* to clarify, as it must, that the Roxane approval is legally ineffective.

<sup>5</sup> Approval, here, being distinct from “effective approval.”

<sup>6</sup> Under §505(j), Roxane would have had to establish bioequivalence to Purdue’s products – a showing it has apparently not made.

FDA regulations, however, forbid applicants to market nonequivalent duplicates through an application that is covered by §505(b)(2) because it does not stand completely on its own merits.

**c. FDA Should Have Refused To File The Roxicodone™ Application Because It Does Not Contain Data To Show How The Proposed Roxane Products Compare To The Previously Approved Purdue OxyContin® Products**

Similarly, if the Roxicodone™ application had been properly presented by Roxane and processed by FDA as a §505(b)(2) application, FDA regulations would also have required Roxane to show that its 10 mg product was at least as bioavailable as the 10 mg OxyContin® product. This requirement appears at 21 C.F.R. §314.54(b), which disallows the submission of a 505(b)(2) application for a drug “whose only difference from the reference listed drug is that: (1) [t]he extent to which its active ingredient(s) is absorbed . . . is less than that of the reference listed drug; or (2) [t]he rate at which its active ingredient(s) is absorbed . . . is unintentionally less than that of the reference listed drug.” As explained by FDA, the purpose of this requirement is clear:

“To allow [a less bioavailable] drug to be approved under section 505(b)(2) would thwart Congress’ clear intention to require that a duplicate of a listed drug be shown to be bioequivalent to that listed drug.” (54 Fed. Reg. at 28892.)

The Roxicodone™ SBA shows no evidence that Roxane ever conducted or submitted to FDA any comparative bioavailability studies between Roxane’s proposed 10 mg tablet and the previously approved Purdue OxyContin® 10 mg tablet. Without such evidence, there is no way Roxane could have demonstrated compliance with 21 C.F.R. §314.54(b) for its 10 mg strength if its NDA had been properly characterized as a 505(b)(2) application.

The same considerations should also have precluded the filing of Roxane’s application with respect to the 30 mg tablet. Without comparative data to show that Roxane’s 30 mg tablet exhibits higher bioavailability than the previously approved 20 mg OxyContin® tablet, and less bioavailability than the previously approved 40 mg OxyContin® tablet, 30 mg of Roxidocone™ may turn out to supply a higher dose than 40 mg of OxyContin® or a lower dose than 20 mg of OxyContin®. Thus, FDA’s approval of the 30 mg Roxicodone™ product leaves physicians and pharmacists to guess (or, more likely, leaves them unaware of the question) whether the labeled strengths of different brands of extended release oxycodone tablets reflect at all the relative potency of the products. As FDA explained in a similar context:

“FDA hopes that designating a single reference listed drug against which all generic versions must be shown to be bioequivalent will avoid possible significant variations among generic drugs and their brand name counterparts. Such variation could result if generic drugs established bioequivalence to different reference listed drugs.” (57 Fed. Reg. at 17954.)

Before the Roxicodone™ NDA may be granted effective approval, these issues of the comparative bioavailability of the Roxane products to the previously approved OxyContin® products must be addressed and properly resolved.

### **3. Roxane Must Make Appropriate Certifications With Regard To The Purdue Patents**

FFDCA §505(b)(2) itself requires applicants who submit NDAs described in that section to make one of four certifications with respect to each patent covering previously approved drug products whose studies were relied upon, in whole or in part, as a basis for the new submission. By ignoring the §505(b)(2) status of its application, and by virtue of FDA’s apparent failure to require it to correct that omission, Roxane was able to pursue effective approval of its application without making any certifications whatsoever with respect to Purdue’s patents.<sup>7</sup> The effect, most importantly, with respect to Purdue, is that Purdue has been denied the explicit statutory entitlement afforded to it by FFDCA §505(c)(3)(C) to a 30 month stay of the Roxane approvals in the event that Roxane seeks to market the Roxicodone™ products prior to the expiration of the Purdue patents. (That 30 month stay would be triggered by Roxane’s notice to Purdue of its filing of a “Paragraph IV” certification and Purdue’s filing of a patent infringement suit within 45 days of such notice. Having made no certification, however, Roxane provided Purdue with no such notice.)

As set forth in the discussion above, Roxane’s application cited and clearly relied on, at least in part, 1) clinical data on oxycodone generated by others, including published clinical data on extended release oxycodone generated by Purdue, and to which Roxane had no right of reference and 2) toxicology and special population data that FDA had previously

---

<sup>7</sup> In this regard, Section 13.0 of Roxane’s NDA, a copy of which was included in the SBA, contains what appears to be an inaccurate and incomplete statement denying the existence of patents “with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of Roxicodone SR™.” Through the Orange Book and otherwise, Roxane was fully aware of the patents covering Purdue’s sustained release oxycodone preparations and should have filed their patent numbers and expiration dates with the FDA under §505(b)(1) and, as a §505(b)(2) applicant, should have provided certifications thereto.

required Purdue to generate and submit on its OxyContin® products. Thus, a certification by Roxane is legally required by §505(b)(2) with respect to each of the Purdue patents covering OxyContin® as a prerequisite to the filing and approval of the Roxane application. As FDA is fully aware, the patent certification requirements of the 1984 Amendments to the FFDCA were a lynchpin of the 1984 compromise that led to the grant of FDA's authority to approve generic drugs through lower-cost application processes. Compliance with those requirements is critical to the maintenance of the effective incentives for innovation that the 1984 amendments were designed to protect. Purdue is entitled to and demands that protection, and FDA has an obligation to assure that it is provided.

**C. Environmental Impact**

Categorical exclusion is claimed under Section 25.30(h) of the regulations.

**D. Economic Impact**

Economic information will be submitted if requested by the Commissioner.

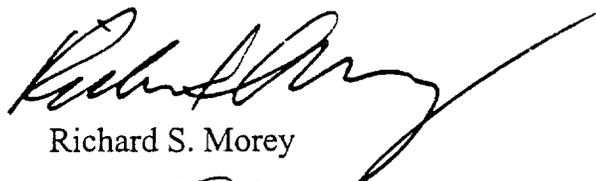
**E. Certification**

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



Alan H. Kaplan



Richard S. Morey



Peter R. Mathers



**DECLARATION OF JOSEPH C. TIGNER, Ph.D.**

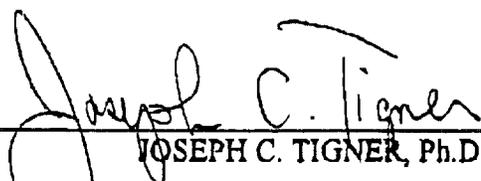
I, JOSEPH C. TIGNER, Ph.D., declare that:

1. I am an employee of Purdue Pharma L.P. ("Purdue"). My title is Senior Director, Drug Safety Evaluation.
2. I joined Purdue in March, 1991. Since then, I have been in charge of Purdue's pre-clinical toxicology program.
3. I earned a BA from Brooklyn College in 1967, a Master's Degree from University of Oregon in 1971, and a Ph.D. from Cornell University in 1978.
4. Since earning my Ph.D. in 1978, I have worked for various pharmaceutical companies as a toxicologist. I attach a copy of my resume as Exhibit A.
5. I oversaw Purdue's pre-clinical toxicity program for OxyContin® Tablets ("OxyContin®") in its entirety from 1993 to 1995. I was also responsible for writing the pharmacology/toxicology section of the New Drug Application for OxyContin®.
6. In performing my responsibilities, I was required to meet, discuss and correspond with FDA regarding the pre-clinical toxicity program for OxyContin®. I dealt directly with Dr. Curtis Wright, the head of the project for FDA, and Dr. Belinda Hayes, FDA's toxicologist on the Project.
7. In my meetings, discussions and correspondence with FDA, FDA made clear that in order to obtain approval for OxyContin®, Purdue would be required to perform certain reproductive toxicity (Segment II) studies on rats and rabbits with oxycodone hydrochloride. The purpose of these teratology studies was to determine the potential birth defects that may result in animals which are given the drug. Specifically, FDA and I discussed the need to do new toxicity studies in a face-to-face meeting on June 23, 1993. Dr. Hayes and I subsequently agreed upon the details of the studies that the FDA required us to perform.

8. The program consisted of six studies. The first two studies were range-finding studies in non-pregnant female animals of each species. The purpose of those studies was to estimate doses to be used in pregnant animals in the next set of studies. The third and fourth studies were range-finding studies in pregnant female animals of each species. The purpose of those studies was to establish doses to be used in the definitive or main Segment II studies in pregnant animals. The fifth and sixth studies were the definitive (and more extensive) studies in pregnant animals of each species. All of the studies were performed in accordance with FDA guidelines and requirements. Dr. Hayes concurred in advance with the specific experimental designs and doses for the reproductive toxicity studies. The completed studies were submitted to the NDA in 1995.

9. I estimate that the reproductive toxicity program took approximately one year to complete and cost roughly \$200,000.

I hereby declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

  
JOSEPH C. TIGNER, Ph.D.

Executed on this 17<sup>th</sup> day of May, 1999

RESUME

JOSEPH C. TIGNER, Ph.D.

Home Address:

1 Santa Lane  
New Milford, CT 06776  
Tel: (860) 354-8322

Business Address:

Purdue Research Center  
444 Saw Mill River Road  
Ardsley, New York 10502  
Tel: (914) 709-2376

PROFESSIONAL EXPERIENCE

1997 - Present

**Senior Director, Department of Drug Safety  
Evaluation**  
Purdue Pharma L.P.

1991 - 1997

**Director, Department of Drug Safety  
Evaluation**  
Purdue Pharma L.P.  
Purdue Research Center  
444 Saw Mill River Road  
Ardsley, New York 10502

The primary responsibility of this position is managing the department of Drug Safety Evaluation. The department has responsibility for supporting international as well as domestic toxicology programs. This includes designing, overseeing and reporting nonclinical toxicology/safety pharmacology studies (including acute, subchronic, chronic, teratology, mutagenicity, and carcinogenicity studies), environmental assessment studies, pharmaceutical products; selecting contract laboratories to perform nonclinical toxicology, environmental assessment, and safety pharmacology studies and monitoring their activities; presenting data to management, colleagues, and regulatory agencies. Writing INDs/NDAs/MAA Expert Reports; meeting with regulatory agencies in the US (FDA) and Europe to discuss regulatory submissions.

Other responsibilities have included: overseeing nonclinical pharmacology testing; overseeing microbiological assays; evaluating potential new licensing candidates; overseeing the industrial hygiene/occupational health program of Purdue Research Center (this includes compliance with OSHA as well as local regulations); budget management for the drug safety and OSHA compliance programs; generation of SOPs; and initiating and managing a pilot in-house vivarium.

The spectrum of pharmaceutical classes has included delayed-release formulations, local anesthetics, anti-inflammatory, anti-neoplastic, bronchodilatory, opioid analgesic (oral and transdermal) and antidiabetic (Type II) drugs, a monoclonal antibody, and OTC topical antiseptics.

1987 - 1991

**Senior Principal Toxicologist**

Toxicology and Safety Assessment

Department

Boehringer Ingelheim Pharmaceuticals, Inc.

90 East Ridge Road,

Ridgefield, Connecticut 06877

Responsibilities included the establishment, development and management/supervision of new in-house toxicology and clinical pathology laboratories and the management of studies conducted at contract laboratories. This experience involved budget management, laboratory design, and staffing of the new laboratory; initiating a GLP training program and a new SOP system; presentations discussions, and correspondence with the FDA; initiating and validating a new computerized data collection system for toxicology; designing toxicology/safety programs for a variety of products including pulmonary, antiviral and biotechnology-derived (recombinant) pharmaceuticals; and being the toxicology representative on the company's Animal Care and Use Committee.

1978 - 1987

**Toxicology Unit Supervisor**

Drug Safety Evaluation Section

Wyeth laboratories, Inc., Paoli, Pennsylvania

Responsibilities included being Study Director and staff toxicologist in charge of both supervisory and non-supervisory technical staff.

Experience in this position:

Designing and preparing experimental protocols and supervising the conduct of acute, subchronic and chronic drug safety evaluation studies, oncogenicity studies, ocular, dermal and intramuscular irritation, pharmacopeial safety, phototoxicity and dermal hypersensitization studies.

Developing protocols for, initiating and monitoring research performed at contract laboratories. This has included inhalation studies, intravenous infusion as well as subchronic, chronic and oncogenicity studies.

Evaluation and interpretation of data.  
Preparation of final toxicology reports and combined toxicology-pathology reports.  
Preparation of summaries of preclinical studies for IND and NDA submissions.

Hiring and training technical staff and assuring that preclinical toxicity studies were conducted in compliance with Good Laboratory Practice regulations.

Examining the toxicity/safety of a wide variety of pharmaceutical entities, including vaccines, antibiotic, anti-inflammatory, cardioactive, CNS, and hormonal products and a Biotechnology-derived peptide.

1972 - 1978

**Research Assistant/NIH Predoctoral Trainee**

Division of Nutritional Sciences  
Cornell University, Ithaca, New York

Responsibilities and experience included designing, performing and reporting pre-and post-natal nutritional studies, teratological studies, studies of drug-induced vitamin deficiency in laboratory animals. Performing biochemical assays for serum and tissue metabolites, serum drug levels and dietary quality. Use of computerized statistical packages. Supervising undergraduate students in teratology and metabolic chemistry. Other activities included tenure as President of the Graduate Nutrition Club and Chairperson of the Cornell Graduate Activities Funding Commission.

1967 - 1971

**Research Assistant/NIMH Predoctoral Trainee**

Department of Psychology  
University of Oregon, Eugene, Oregon

Responsibilities and experience included designing, performing and reporting behavioral studies (maze learning, shock avoidance, open field, and maternal behaviors). Performing neurosurgery in rodents using stereotaxic and non-stereotaxic procedures.

**OTHER EXPERIENCE**

1993 - 1994

**Adjunct Assistant Professor of  
Pharmacology**

Massachusetts College of Pharmacy and  
Allied Health Sciences  
Boston, Massachusetts

**PROFESSIONAL EDUCATION**

1978

Doctor of Philosophy, Cornell University  
Major: Nutritional Sciences  
Minors: Pharmacology, Physiology  
Doctoral Dissertation: *The Relation of  
Meternal Folacin Status and Intake of  
Diphenylhydantoin to Fetal Development and  
Maternal-Fetal Folacin Stores in the Albino  
Rat.*

Master of Arts, University of Oregon  
Major: Physiological Psychology

Bachelor of Arts (*cum laude*), Brooklyn College  
Major: Psychology

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American College of Toxicology  
(elected member of the Education Committee, 1993 - 1995)

Mid-Atlantic Chapter of the Society of Toxicology  
(Member of the Program Committee, 1987 - 1990)

Northeast Chapter of the Society of Toxicology  
(Organized the Fall 1990 Symposium on Nutritional Toxicology in Worcester,  
Massachusetts)

Society of Toxicology of Canada

Society of Toxicology (Member of the Committee on Animals in Research, 1992 - 1995)

American Association of Clinical Chemistry  
(Animal Clinical Chemistry Division)

American Chemical Society  
(Division of Chemical Health and Safety)

International Life Sciences Institute (ILSI). Member of the validation committee for  
transgenic animals as alternative models of carcinogenicity.

## PUBLICATION

**Srinivasan, V., Talay, S., Andrews, J., Miotto J., Savidge, S., Stadnicki, S., Tigner, J., Tonelli, F.:** Hydromorphone Pharmacokinetics in the Pregnant Rat and Rabbit: Comparison with Human Exposure. Poster presented at the American Association of Pharmaceutical Sciences, San Francisco, CA., November 1998.

**Curley, J.M., Castillo, J., Hotz, J., Uezono, M., Hernandez, S., Tigner, J., Chasin, M., Langer, R., Berde, C.:** Prolonged regional nerve blockade: Injectable biodegradable bupivacaine-polyester microspheres. *Anesthesiology*, 1996, 84, 1401.

**Castillo, J., Curely, J.M., Hotz, J., Uezono, M., Tigner, J., Chasin, M., Langer, R., Berde, C.:** Glucocorticoids prolong rat sciatic nerve blockade *in vivo* from bupivacaine microspheres. *Anesthesiology*, 1996, 85, 1157.

**Tigner, J.C., Blair, M., Rajasekaren, D. and Nair, K.P.:** Preclinical Systemic Toxicity of PF-10,40HCl, a Novel Anti-inflammatory. Abstract presented at the annual meeting of the Society of Toxicology, Dallas, Texas, 15 March 1994.

**Buchanan, L., Galarneau, N., Huard, L., Huard, G., Duguay, G., and Tigner, J.C.:** *In Vivo* and *in Vitro* Assessments of PF 10,040HCl on Rat Hepatic Enzyme Induction. Abstract presented at the annual meeting of the Society of Toxicology, Dallas, Texas, 15 March 1994.

**Tigner, J.C. and Roe, D.A.:** Tissue Folicin Stores in Rats Measured by Radioassay. *Proc. Soc. Exper. Biol. Med.*, 160, 445-448, (1979).

**Tigner, J.C. and Roe, D.A.:** Relationship Between Dietary and Tissue Folicin in Pregnant Rats and Their Fetuses. *Fed. Proc.*, 27, 494, (1978) (Abstract).

**Tigner, J.C. and Roe, D.A.:** Folicin Deficiency in Rat Tissues Measured by Competitive Protein Binding Assay, *Fed. Proc.*, 36, 1120, (1977) (Abstract).

**Tigner, J.C. and Barnes, R. H.:** Effect of Postnatal Malnutrition on Plasma Corticosteroid Levels in Male Albino Rats. *Proc. Soc. Exper. Biol. Med* 149, 80-82, 1975.

**Tigner, J.C.:** The Effects of Dorsomedial Thalamic Lesions on Learning, Reversal and Alternation Behavior in the Rat. *Physiol. Behav.*, 12,13-17, (1974).

**Tigner, J.C. and Wallace, R.J.:** Hoarding of Food and Non-Food Items in Blind, Anosmic, and Intact Albino Rats. *Physiol. Behav.*, 8, 927-936, (1972).

**Wallace, R.J. and Tigner, J.C.:** Effect of Cortical and Hippocampal Lesions on Hoarding Behavior in the Albino Rat. *Physiol. Behav.*, 8, 937-942, (1972).

**Tigner, J.C.:** Impairment of One-Way active Avoidance in Rats with Habenular and Dorsomedial Thalamic Lesions. *Psychonom. Sci.*, 27, 7-8, (1972)



90.000 001

**D R A F T**  
MEETING MINUTES

OXYCODONE ACROCONTIN™ (OXYCONTIN™ TABLETS)  
PROJECT MANAGEMENT MEETING - RDC SITE

Wednesday, June 23, 1993  
13:30 - 17:00  
Research Data Corporation  
5615 Fishers Lane  
Rockville, Maryland 20857  
(301)230-1335

FDA Representatives:

Dr. Curtis Wright - Medical Review Officer  
Dr. Dennis Bashaw - Biopharmaceutics  
Ms. Mary Owens - Consumer Safety Officer  
Dr. Belinda Hayes - Pharmacology/Toxicology  
Dr. Pat Muturu - Chemist  
Dr. V. Bhavngri - Chemist  
Dr. D.H. Leung - Statistician

Representatives of The Purdue Frederick Company (PF):

Dr. David Benziger - Pharmacokineticist  
Dr. James Conover - Project Manager, Regulatory  
Dr. Ronald Fitzmartin - Statistician  
Dr. Paul Goldenheim - Purdue Research Center  
Dr. Robert Kaiko - Medical  
Mr. Benjamin Oshlack - Pharmaceutical Development  
Dr. Philip Palermo - Chemist  
Dr. Robert Reder - Medical  
Ms. Lee Ann Storey - Project Manager, Regulatory  
Dr. Joseph Tigner - Pharmacology/Toxicology

**D R A F T**

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

Pre-Clinical Pharmacology/Toxicology

Participants:	Pharmacology/Toxicology	Dr. B. Hayes Ms. M. Owens Dr. J. Tigner
	CMC (Impurities Issue)	Dr. V. Bhavagri Dr. P. Maturu Dr. P. Palermo Dr. J. Tigner

The overhead/material shown and/or discussed in the Pre-Clinical Pharmacology/Toxicology working group are attached in APPENDIX 3.

**SUMMARY**

- 1)
- 2) Nonclinical Toxicology: It was agreed that the nonclinical safety data for the excipients, including Eudragit RS/PM, indicate reasonable safety for the intended pharmaceutical use of the product. It was also agreed that oxycodone is an old drug in which the human toxicity profile is well-known. The FDA is somewhat concerned, however, that the PF-sponsored safety studies in mice are not sufficient to support an NDA for the final product. It was stated that even with an old drug such as this, if the nonclinical toxicity is sparse, the agency has been asking for some preclinical toxicology. [Dr. Wright amplified this position at the Wrap-Up Session. He stated that he thought that the agency would want us to do an abbreviated toxicology package such as a subacute study]. It was agreed that Dr. Hayes would call Dr. Tigner on June 30, 1993 to further discuss this matter. During this session, Dr. Tigner gave Dr. Hayes copies of written and tabulated material.

[Subsequent telephone conversations were held on June 30 and July 7. As part of those conversations, the FDA is requesting that PF do Segment II teratology studies in rats and rabbits. The protocols will be discussed with the FDA prior to doing the studies.]

**D R A F T**

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

Clinical

Participants:       Dr. R. Rader  
                      Dr. C. Wright  
                      Dr. R. Fitzmartin  
                      Dr. D.H. Leung  
                      Ms. M. Owens  
                      Ms. L. A. Storey

Drs. Rader and Fitzmartin reviewed the core clinical program and the additional clinical study program. The overheads/material shown and/or discussed in the Clinical working group are attached in APPENDIX 4.

## SUMMARY

1)

2)

3)

4)

5)

90.000 010

# D R A F T

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

## Clinical

6)

7)

8)

9) Usage and/or PK Data: The NDA and/or initiated Phase IV studies are to include usage data and/or PK in the following populations: women, elderly, pediatric, renal impaired and hepatic impaired

10)

11)

12)

13)

14)

15)

90.000 011

# DRAFT

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

## Pharmacokinetics/Biopharmaceutics

Participants:           Dr. D. Bashaw  
                          Dr. D. Benziger  
                          Dr. R. Kaiko

The overheads/material shown and/or discussed in the Pharmacokinetics/Biopharmaceutics working group are attached in APPENDIX 5.

### SUMMARY

1)

2)

3)

D R A F T

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

Pharmacokinetics/Biofarmaceutics

4)

5)

6)

7)

8)

## D R A F T

FDA Meeting - June 23, 1993  
Oxycodone Controlled-Release Tablets  
IND #29,038

---

Pharmacokinetics/Bioequivalents

- 9) Special Studies: We presented our plans for examining the kinetics of oxycodone in special populations. The recently completed study comparing young vs elderly included women which made this study acceptable. The other planned studies include kinetics in renal and hepatic impairment. These studies should include women. It was agreed that the results of the elderly and renal studies would be available in the NDA. Dr. Bashaw concurred that enrollment may be prolonged in the hepatic study so that it may not be available until after approval. He requested that we submit any available data for review even if the study is not complete and that we supply in writing the estimated completion date. There have been instances where Sponsors have committed to conducting special studies in Phase-IV but have failed to follow through in an expeditious manner. This is the rationale for obtaining our commitment to complete the hepatic study in a specific time frame (assuming its not done by approval date).

10)

11)

12)



DECLARATION OF ROBERT F. REDER, M.D.

I, ROBERT F. REDER, M.D., declare that:

1. I am a Vice President for Purdue Pharma L.P. and Vice President, Medical Director for The Purdue Frederick Company (collectively "Purdue"). I received my B.A. from the University of Wisconsin in 1969 and my M.D. from the Mount Sinai School of Medicine of the City University of New York in 1973. Since 1983, I have practiced pharmaceutical medicine in the pharmaceutical industry, especially in connection with the clinical aspects of drug development and marketing. My particular focus has been drug development in the United States. I attach a copy of my curriculum vitae as Exhibit A to this Declaration.

2. I joined Purdue on April 1, 1992. One of my principal responsibilities at that time was to head the clinical development program for OxyContin® Tablets ("OxyContin®") (oxycodone hydrochloride controlled release tablets).

3. My first substantial interaction with the U.S. Food and Drug Administration ("FDA") in connection with the development of OxyContin® was a meeting held on June 3, 1992 at FDA headquarters. At the time OxyContin® was not a marketed product and held investigational status (IND). Several of my colleagues from Purdue and I met with FDA officials on the project, including Dr. Curtis Wright and Dr. Dennis Bashaw. FDA had reviewed our clinical development program for OxyContin®. They told us that our program was headed toward disastrous straits. They said the program would take FDA five years to review and, in the end, would probably not be approved. FDA recommended that instead we should work together to establish a program that FDA could find acceptable. FDA advised that the revised clinical program should include significantly more diversity in the clinical studies and much more pharmacokinetic information, especially in selected populations.



4. Purdue accepted FDA's advice. After that June 1992 meeting, we dramatically restructured our clinical program and planned substantially more pharmacokinetic work, including studying the effect of the drug in patients of selected populations. In addition, as requested we became much more interactive with FDA regarding clinical development issues surrounding this product.

5. During the next year or two, while working closely with FDA, I came to the clear understanding that in order to obtain approval for OxyContin®, Purdue needed to provide FDA substantially new and additional information, including among other things, how the drug behaved in patients who had impairment of kidney (renal) function and in patients who had impairment of hepatic (liver) function. Indeed, my understanding of the FDA advice was that FDA would not accept our New Drug Application (NDA) for OxyContin® if we did not include such data from both of these special populations (renal and hepatic). Based on this recommendation, Purdue initiated studies in renal and hepatic special populations and submitted data from these studies as part of the NDA.

6. To the best of my knowledge, Purdue has never granted to Roxane Laboratories, Inc. or any other pharmaceutical research and development company in the United States, a right of reference concerning any of our clinical or pharmacokinetic data regarding OxyContin®, including our data on renal-impaired or hepatic-impaired patients.

I hereby declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.



---

Robert F. Reder, M.D.

Executed on this 14<sup>th</sup> day of May, 1999.

Curriculum Vitae

Robert F. Reder, M.D.  
Vice President, Medical Director

The Purdue Frederick Company  
100 Connecticut Avenue  
Norwalk, CT 06850  
Telephone (203) 854-7220  
Fax (203) 831-9659

*Education:*

1969	B.A.	University of Wisconsin Madison, Wisconsin
1973	M.D.	Mount Sinai School of Medicine of the City University of New York New York, New York

### Pharmaceutical Industry Experience

1995 - Vice President, Medical Director  
1991 - 1995 Medical Director  
The Purdue Frederick Company/Purdue Pharma L.P., Norwalk, Connecticut

#### Responsibilities

- Senior management team
- Medical officer responsible for phases I-IV clinical trials
- Project leader for IND/NDA programs
- Core member high performance drug development team
- Member of the interactive IND/NDA process evaluation project with FDA
- Medical department GCP implementation
- Management of the Department of Biostatistics and Clinical Data Management
- Evaluation of corporate licensing opportunities
- Patent development

#### Therapeutic Areas

Analgesics, antiseptics, bronchodilators, cardiac antiarrhythmics, laxatives, local anesthetics, non-steroidal anti-inflammatory drugs, phosphodiesterase inhibitors

#### Product Approvals

- Betadine® Antibiotic with Moisturizer
- Betadine® Soft Scrub
- BioFill® Cellulose Wound Dressing [510(k)]
- Children's Senokot®
- DHC™ plus Capsules (88-584)
- MS Contin® 200 mg Tablets (19-516)
- OxyContin® Tablets (20-553)
- OxyIR® Capsules

1990 - 1991 Vice President, Clinical Research  
Sanofi Pharmaceuticals, Inc., New York, New York

#### Responsibilities

- Chief medical officer responsible for biostatistics and phase I, II and III clinical trials activities in the U.S. and Canada.
- Responsible for medical aspects of new IND files in development.
- Participant in Sanofi international development teams.
- Evaluation of product license candidates and new business opportunities.
- Involvement in the Sanofi/Sterling-Winthrop joint venture discussions and transition. Sanofi projects transferred to Sterling-Winthrop. Sanofi Pharmaceuticals, Inc. closed effective 31 December 1991.

#### Therapeutic Areas

Anti-anginal, antibiotics, anti-cancer, antiepileptic, antihypertensive, antimalarial, anti osteoporosis - IND and PNDS active, antiplatelet - IND and PNDS active, cardiac antiarrhythmics - PNDS active, low molecular weight heparin - IND active, T-cell depletor - IND active, transdermal hormone - IND active

1987 - 1990      **Vice President, Medical Affairs**  
1984 - 1987      **Director, Medical Affairs Department**  
                    Knoll Pharmaceuticals, a subsidiary of Knoll AG and unit of BASF, Whippany, New Jersey

**Corporate Responsibilities**

Member, Administrative Committee - Responsible for daily operations and business strategy for the company  
Employee Health/Occupational Safety Group  
Member - Health and Safety Committee  
Co-member - Ecology Committee  
Medical Review of Activities of Knoll - Canada  
Expert testimony in criminal actions involving narcotic prosecutions/products liability litigation

**Department Responsibilities**

Medical content of product launch, sales, sales training and advertising materials  
Medical support for marketed products  
Medical portions of annual reports and support for regulatory strategy  
Assembly of clinical portions of INDs and NDAs  
Adverse event reporting  
Medical information  
Package insert revision  
Medical writing  
Patent development  
Medical oversight of medical research (Immunology, Oncology, ONS, CV and pre-clinical) - 1988

**Therapeutic Areas**

Analgesics, antiarrhythmics, antihypertensives, wound debridement

**Product Approvals**

Dilaudid® - HP - Analgesic (19-034)  
Isoptin ®SR 240 mg tablets - Antihypertensive; Isoptin SR 180 mg tablets (19-152)  
Isoptin ®IR - Antihypertensive and antiarrhythmic indications (18-593)  
Rythmol®-Ventricular antiarrhythmic (19-151)  
Vicodin ®ES - Analgesic (89-736)

1983 - 1984      **Associate Director Cardiovascular Clinical Research**  
                    Bristol Myers Co., Evansville, Indiana

**Responsibilities**

d-Sotalol      Clinical Project Director phases I and II development, worldwide  
Encainide      Associate Clinical Project Director: U.S. NDA submission (18-981) and ongoing clinical studies

**Clinical Practice Experience - Academic Appointments**

1979-80	Assistant Professor of Pediatrics	College of Physicians and Surgeons of Columbia University New York, New York
1980-83	Assistant Professor of Pediatrics	Mount Sinai School of Medicine of the City University of New York New York, New York
1992-95	Professorial Lecturer	Mount Sinai School of Medicine of The City University of New York New York, New York

**Clinical Practice Experience - Hospital Appointments**

1979-80	Assistant Attending Physician	Columbia-Presbyterian Medical Center New York, New York
1980-82	Assistant Attending Physician	Mount Sinai Medical Center New York, New York
1982-83	Associate Attending Physician	Mount Sinai Medical Center New York, New York
1993-95	Acting Clinical Assistant	Mount Sinai Medical Center New York, New York

**Qualifications**

1974	Diplomate	National Board of Medical Examiners, No. 130790
1978	Diplomate	American Board of Pediatrics, No. 022054
1979	Diplomate	American Board of Pediatrics, Sub-Board of Pediatric Cardiology, No. 525
1974	Medical Licensure	New York No. 120674
1974	Medical Licensure	Washington No. 14090
1983	Medical Licensure	Indiana No. 32920

Qualifications (*continued*)

1995	Medical Licensure	Connecticut No. 034295
1997	DEA	AR7339852
1984	AMA Physician's Recognition Award	
1987	AMA Physician's Recognition Award	
1990	AMA Physician's Recognition Award	
1993	AMA Physician's Recognition Award	
1996	AMA Physician's Recognition Award	

Societies

American Academy of Pediatrics, Fellow  
Member Section on Cardiology  
American Academy of Pharmaceutical Physicians  
Vice President, Membership Development 1996 -  
American Association for the Advancement of Science - Inactive  
American College of Cardiology, Fellow  
American College of Chest Physicians, Fellow  
American College of Clinical Pharmacology, Fellow  
American Federation for Clinical Research - Inactive  
American Heart Association - Inactive  
Member Council on Cardiovascular Diseases in the Young  
American Medical Association  
American Pain Society  
American Society for Clinical Pharmacology and Therapeutics  
American Society for Pharmacology and Experimental Therapeutics  
American Society of Hypertension - Inactive  
Associated Alumni of the Mount Sinai Hospital and the Mount Sinai School of Medicine  
Association for Pharmacoeconomics and Outcomes Research  
College on Problems of Drug Dependence, Inc. - Associate Member  
Drug Information Association - Inactive  
Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom  
International Association for the Study of Pain  
International Narcotic Enforcement Officers Association, Inc.  
International Society for Heart Research, Member, American Section - Inactive  
International Society on Hypertension in Blacks, Charter Member - inactive  
The New York Academy of Medicine, Fellow  
The New York Academy of Sciences - Inactive  
The New York Cardiological Society, Fellow - Inactive

### Traineeship

1973-74	Intern in Pediatrics	Children's Orthopedic Hospital and Medical Center Seattle, Washington
1974-75	Resident in Pediatrics	Mount Sinai Hospital New York, New York
1975-77	Fellow in Pediatric Cardiology	Mount Sinai Hospital New York, New York
1977-79	Staff Associate Department of Pharmacology	College of Physicians and Surgeons of Columbia University New York, New York
1978-79	Visiting Fellow in Pediatric Cardiology	Columbia-Presbyterian Medical Center New York, New York

### Grants

1977-79	NIH Training Grant HL-07271
1978-80	Fellow of the Leopold Schepp Foundation
1979-80	Molly Berns Senior Investigator of the New York Heart Association
1979-80	Coordinator, NIH Training Grant HL-07419

### Committee Memberships/Hospital Positions

1980-83	Director, Pediatric Cardiology Cardiac Catheterization Laboratory, Mount Sinai Medical Center
1981-83	Medical Standards and Procedures Committee of the Medical Board of the Mount Sinai Medical Center
1980-83	Member, The Association of the Attending Staff of Mount Sinai Medical Center
1985	Grant Review NIH
1989	Member, Analgesic Guidelines Committee. American Society for Clinical Pharmacology and Therapeutics.

### Patents

Methods for Providing Safe Local Anesthesia, Serial No. 60/020,315, Filing Date: June 24, 1996.

### Review Articles, Chapters, Books

1. Reder RF, Rosen MR: The role of the sympathetic nervous system in sudden cardiac death. *Drug Therapy* 8:41-48, 1978.

**Review Articles, Chapters, Books (continued)**

2. Rosen MR, Hordof AJ, Reder RF, Danilo P Jr: Age-related and disease-related changes in cardiac electrophysiologic properties. *From Cardiac Arrhythmias: Electrophysiology, Diagnosis and Management*. Narula, O (Ed), William and Wilkins, Baltimore, pp 32-39, 1979.
3. Reder RF, Rosen MR: Basic Electrophysiologic Principles: Application to Treatment of Dysrhythmias. In *Pediatric Cardiac Dysrhythmias*, Gillette PC and Garson A (Eds), Grune and Stratton, NY, pp 121-143, 1981.
4. Rosen MR, Reder RF: Does Triggered Activity Have a Role in the Genesis of Cardiac Arrhythmias? *Ann Int Med* 94:794-801, 1981.
5. Reder RF and Rosen MR: Mechanisms of cardiac arrhythmias. *Cardiovasc Rev Reports* 2:1007-1012, 1981
6. Reder RF, Rosen MR: Delayed after depolarizations and clinical arrhythmogenesis. In *Normal and Abnormal Conduction in the Heart*, Paes de Carvalho A, Hoffman BF and Lieberman M (Eds), Futura Publishing, Mount Kisco, NY, 1982, pp 449-460.
7. Rosen MR, Reder RF: Electrophysiology of the fetal and neonatal heart. In *Perinatal Cardiovascular Function*, Gootman N and Gootman PM (Eds), Marcel Dekker, Inc, NY, pp 201-225, 1983.
8. Kupersmith J, Bunt PJ, Reder RF: Newer antiarrhythmic drugs. *Primary Cardiology, Supplement, No 2*, pp 164-167, 1983.
9. Kupersmith J, Reder RF: Amiodarone: A Review. *Primary Cardiology* 10(7): 116-126, 1984.
10. Kupersmith J, Reder RF, Slater, W: New antiarrhythmic drugs. *Cardiovasc Rev Rep* 6(1):35-56, 1985.
11. Reder RF, Binah O, Danilo P Jr: Autonomic effects in the developing heart. In *Developmental Neurobiology of the Autonomic Nervous System*, Goodman PM (Ed), Humana Press, Inc, Clifton, NJ, pp 193-210, 1986.

**Original Articles**

1. Reder RF, Dimich I, Steinfeld, L, Litwak RS: Left Ventricle to aorta valved conduit for relief of diffuse left ventricular outflow tract obstruction. *Am J Cardiol* 39:1068-1072, 1977.
2. Reder RF, Yeh HC, Dimich I, Steinfeld L: Serial echocardiography of the aortic valve in bacterial endocarditis - a case report. *Mt Sinai J Med* 44:521-526, 1977.
3. Steinfeld L, Dimich I, Reder R, Cohen ML, Alexander H: Sphygmomanometry in the pediatric patient. *J Pediatr* 92:934-938, 1978.
4. Reder RF, Dimich I, Cohen ML, Steinfeld L: Evaluating indirect blood pressure techniques - a comparison of three systems in infants and children. *Pediatr* 62:326-330, 1978.
5. Rosen MR, Reder RF, Hordof AJ, Davies M, Danilo P: Age-related Changes in Purkinje fiber action potentials of adult dogs. *Circ Res* 43:931-939, 1978.
6. Nichols EA, Reder RF: Familial mediterranean fever - a case report. *Am J Dis Child* 132:1209-1210, 1978.
7. Reder RF, Danilo P, Rosen MR: Effects of pirlmenol HC1 on electrophysiologic properties of cardiac Purkinje fibers. *Eur J Pharmacol* 61:321-333, 1980.

Original Articles (*continued*)

8. Danilo P, Hordof AJ, Reder RF, Rosen MR: Effects of verapamil on electrophysiologic properties of blood superfused cardiac Purkinje fibers. *J Pharmacol Exp Ther* 213:222-227, 1980.
9. Reder RF, Miura DS, Danilo P, Rosen MR: The electrophysiologic properties of normal neonatal and adult canine cardiac Purkinje fibers. *Circ Res* 48:658-668, 1981.
10. Reder RF, Yeh HC, Steinfeld L: Aneurysm of the interatrial septum causing pulmonary venous obstruction in an infant with tricuspid atresia. *Am Hear J* 102:786-789, 1981.
11. Dangman KH, Danilo P, Hordof AJ, Mary-Ravine L, Reder RF, Rosen MR: Electrophysiologic characteristics of human ventricular and Purkinje fibers. *Circulation* 65:362-368, 1982.
12. Reder RF, Brown EG, DeAsla RA, Jurado RA: Thermal skin burns in children from a CO<sub>2</sub> analyzer. *Ann Thorac Surg* 35:329-330, 1983.
13. Reder RF, Camunas JL, Shiang H, Danilo P, Mindich BP: Experimental replacement of canine pericardium. *Mt Sinai J of Med* 50:491-497, 1983.
14. Danilo P Jr, Reder RF, Legato M, Binah O: Fetal canine cardiac Purkinje fibers: electrophysiology and ultrastructure. *Am J Physiol* 246:H250-H260, 1984.
15. Reder RF, Raucher H, Cesa M, Mindich BP: Purulent pericarditis caused by Streptococcus Anginosus - Constellatus - A case report. *Mt Sinai J of Med Vol 51, No 3, June, 1984.*
16. Reder RF, Danilo P Jr, Rosen MR: Developmental changes in alpha adrenergic effects on canine Purkinje fiber automaticity. *Dev Pharmacol Ther* 7:94-108, 1984.
17. Reder RF, Mindich B, Halperin J, Litwak RS, Kupersmith J: Acute effects of oral labetalol on myocardial conduction after coronary artery bypass grafting. *Clin Pharmacol Ther* 35:454-460, 1984.
18. Robinson RB, Reder RF, Danilo P Jr: Preparation and electrophysiological characterization of cardiac cell cultures derived from the fetal canine ventricle. *Dev Pharmacol Ther* 7:307-318, 1984.
19. Halperin JL, Mindich BP, Rothlauf EB, Reder RF, Litwak RS, Kupersmith J: Effects of labetalol on limb hemodynamics in patients following coronary artery bypass graft surgery. *Br J Clin Pharmacol* 21:537-542, 1986.
20. Moak JP, Reder RF, Danilo P Jr, Rosen MR: Development changes in the interactions of cholinergic and beta-adrenergic agonists on electrophysiologic properties of canine cardiac Purkinje fibers. *Pediatr Res* 20(7):613-618, 1986.
21. Thadani U, Prasad R, Hamilton SF, Karpow SA, Reder RF, Teague SM: Isosorbide-5-Mononitrate in angina pectoris: dose response, plasma concentrations and duration of effects following acute therapy. *Clin Pharmacol Ther* 42:58-65, 1987.
22. Thadani U, Prasad R, Hamilton SF, Voyles W, Doyle R, Karpow S, Reder RF, Teague SM: Usefulness of twice-daily isosorbide-5-mononitrate in preventing development of tolerance in angina pectoris. *Am J Cardiol* 60:477-482, 1987.
23. Cubberley RB, Thomas S, Charatan M, Zolli B, Reder RF: Effects of verapamil in black hypertensive patients. *Cardiovasc Rev Reports* 9(5):55-58, 1988.

Original Articles (*continued*)

24. McMahon FG, Reder RF, for the Verapamil SR Study Group: The relationship of dose to the antihypertensive response of verapamil-sustained release in patients with mild to moderate essential hypertension. *J Clin Pharmacol* 29:1003-1007, 1989.
25. Hernandez M, Reder R, Marinchak RA, Rials SJ, Kowey PR: Propafenone for malignant ventricular arrhythmia: An analysis of the literature. *Am Heart J* 121:4(1):1178-1184, 1991.
26. Kaiko RF, Grandy RP, Reder RF, Goldenheim PD, Sackler RS: A bioequivalence study of oral controlled-release morphine using naltrexone blockade. *J Clin Pharmacol* 35:499-504, 1995.
27. Bashaw D, Kaiko RF, Grandy RP, Reder RF, Goldenheim PD, Relative bioavailability of controlled release oral morphine sulfate during naltrexone blockade. *Int J Clin Pharmacol Thera* 33(9):524-529, 1995.
28. Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD: Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Thera* 59:52-61, 1996.
29. Reder RF, Oshlack B, Jahanara MS, Miotto JB, Benziger DD, Kaiko, RF: Steady-state bioavailability of controlled-release oxycodone in normal subjects. *Clin Thera* 18(1):95-105, 1996.
30. Benziger DP, Kaiko RF, Miotto JB, Fitzmartin RD, Reder RF and Chasin M: Differential effects of food on the bioavailability of controlled-release oxycodone tablets and immediate-release oxycodone solution. *J Pharmaceu Sci* 85(4):407-410, 1996.
31. Sunshine A, Olson NZ, Colon, A, Rivera J, Kaiko, RF, Fitzmartin, RD, Reder, RF, and Goldenheim, PD: Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* 36:595-603, 1996.
32. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR; Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol* 42:747-756, 1996
33. Kaplan R, Parris, WCV, Citron, ML, Zhukovsky, D, Reder, RF, Buckley, BJ, Kaiko, RF: comparison of controlled-release oxycodone tablets in patients with cancer pain. *J Clin Oncology* 16:3230-3237, 1998.
34. Parris, WCV, Johnson, BW, Croghan, MK, Moore, MR, Khojasteh, A, Reder, RF, Kaiko, RF, Buckley BJ: the use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. *J Pain and Symptom Management* 16:205-211, 1998.
35. Citron,ML, Kaplan,R, Parris,WCV, Croghan,MK, Herbst,LH, Rosenbluth,RJ, Slagle,NS, Buckley,BJ, Kaiko,RF. Long-Term Administration of Controlled-Release Oxycodone Tablets for the Treatment of Cancer Pain. *Cancer Investigation*, 16(8), 562-571, 1998.
36. Mucci-LoRusso, P, Berman, BS, Silberstein, PT, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain* 2/3:239-249, 1998.
37. Roth, SH, Reder, RF. The role of opioids in the treatment of osteoarthritis. *Resident & Staff Physician* 44(12):31-36, 1998.

### Abstracts

1. Dimich I, Reder RF, Steinfeld L: Cardiovascular effects of maternal methadone addiction in the newborn. *Pediatric Res II(4):338, 1977.*
2. Steinfeld L, Reder RF, Dimich I: Evaluating indirect blood pressure techniques - A comparative study. *Pediatric Res II(4):400, 1977.*
3. Steinfeld L, Reder RF, Dimich I: Evaluating indirect blood pressure techniques - A comparative study. *Circulation 55 & 56 III-20, 1977.*
4. Reder RF, Danilo P, Rosen MR: Effects of CI845 on canine Purkinje fibers with fast and slow response action potentials. *The Pharmacologist 20(3):149, 1978.*
5. Reder RF, Hordof A, Davies M, Danilo P, Rosen MR: Age-related changes in adult canine cardiac Purkinje fiber action potentials. *Circulation 58:II-46, 1978.*
6. Reder RF, Danilo P, Rosen MR: Age-related changes in effects of tetrodotoxin on cardiac Purkinje fibers. *Fed Proc 38(3):880, 1979.*
7. Reder RF, Danilo P, Rosen MR: Effects of Pirmenol hydrochloride on blood-superfused canine cardiac Purkinje fibers. *The Pharmacologist 21:200, 1979.*
8. Danilo P, Reder RF, Mill J, Petrie R: Developmental changes in cellular electrophysiologic characteristics and catecholamine content of fetal heart. *Circulation 59 & 60 (Suppl II) II-50, 1979.*
9. Danilo P, Reder RF, Hordof AJ, Rosen MR: Age-related changes in cellular electrophysiologic properties. *Bull NY Acad Med 55:412-413, 1979.*
10. Reder RF: Age-related changes in the electrophysiologic properties of neonatal and adult canine cardiac Purkinje fibers. *Trends in Pharmacologic Sci 1(5):Jan, 1980.*
11. Reder RF, Miura D, Danilo P, Rosen MR: The electrophysiologic properties of normal neonatal and adult canine cardiac Purkinje fibers. *Am J Cardiol 45:431, 1980.*
12. Reder RF: Effects of maturation on the slow, inward calcium current in the canine heart. *Pediatric Cardiol 1:170, 1979/1980.*
13. Reder RF, Danilo P, Rosen MR: Developmental changes in  $\alpha$ -adrenergic effects on automaticity. *Circulation 62:III-55, 1980.*
14. Rosen MR, Dangman K, Danilo P, Hoffman B, Hordof A, Mary-Rabine L, Reder RF, Reemtsma K: Electrophysiology of human Purkinje and ventricular fibers. *Circulation 62:III-56, 1980.*
15. Reder RF, Danilo P: Effects of tetrodotoxin on fetal canine cardiac Purkinje fibers. *Fed Proc 40:469, 1981.*
16. Robinson RB, Frame LH, Reder RF, Danilo P: Electrophysiologic characteristics of canine cardiac monolayer cultures. *Fed Proc 40:562, 1981.*
17. Danilo P, Reder RF, Garlick P, Rosen MR, Mill J: Effects of sympathectomy on the response to catecholamine of canine Purkinje fibers. *Fed Proc 40:414, 1981.*

Abstracts (continued)

18. Steinfeld L, Rezende J, Nazarian H, Arnon R, Reder RF: Persistent fetal circulation studied by contrast echocardiography. *Pediatr Cardiol* 2(2):175, 1982.
19. Moak JP, Rosen MR, Reder RF, Danilo P Jr: Interactions of isoproterenol and acetylcholine on neonatal and adult canine cardiac Purkinje fibers. *Circulation* 68:III-329, 1983.
20. Halperin JL, Rothlauf EB, Mindich BP, Reder RF, Litwak RS, Kupersmith J: Limb hemodynamic effects of labetalol following coronary bypass surgery. *Clinical Res* 32:173A, 1984.
21. Thadani U, Prasad R, Hamilton S, Karpow S, Reder RF, Teague S: Isosorbide-5-mononitrate in angina pectoris: Does BID dosing schedule prevent development of tolerance? *Clin Invest Med* 9:B55, 1986.
22. Thadani U, Prasad R, Hamilton S, Karpow S, Reder R, Teague S: Isosorbide-5-mononitrate in angina pectoris: Does BID dosing schedule prevent development of tolerance? *Circulation* 74(Suppl II):II-137, Oct 1986.
23. Thadani U, Prasad R, Hamilton S, Karpow S, Reder R, Teague S: Isosorbide-5-mononitrate in angina pectoris: Does BID dosing schedule prevent development of tolerance? Presented to the 9th Asian-Pacific Congress of Cardiology, 1986.
24. Thadani U, Prasad R, Hamilton S, Voyles W, Teague S, Doyle R, Karpow S, Reder R: Duration of effects of Isosorbide-5-mononitrate in angina pectoris. *Clin Pharmacol Ther* 41:183, 1987.
25. Thadani U, Prasad R, Hamilton S, Voyles W, Doyle R, Karpow S, Reder RF, Teague S: Duration of effects of Isosorbide-5-mononitrate in angina pectoris. *JACC Vol 9, p 134A, 1987.*
26. Turek D, Reder R, Karpow S, Baird W: Pharmacokinetic/pharmacodynamic comparison of low and high dose hydromorphone and morphine oral solutions in acute post operative pain. *Clin Pharmacol Ther* 41:229, 1987.
27. Deedwania P, Bittar N, Reder RF, Karpow S, Thadani U: Nitrate Tolerance: Failure of twice daily therapy with isosorbide-5-mononitrate in improving exercise tolerance throughout the dosing intervals. Presented at Xth International Congress of Pharmacology, Sydney, Australia, August 23-28, 1987.
28. Jain AK, McMahon FG, Reder RF, Smith G: A placebo-controlled study of an oral solution of 5 and 10 mg of hydromorphone HCl in post operative pain. *Clin Pharmacol Ther* 45(2):175, 1989.
29. Deedwania P, Bittar N, Reder R, Karpow S, Thadani U: Nitrate tolerance despite high plasma concentrations and 12 hourly treatments with Isosorbide-5-mononitrate. Presented at the IV World Conference on Clinical Pharmacology & Therapeutics, Heidelberg, Germany July 23-28, 1989.
30. Thadani U, Bittar N, Doyle R, Karpow S, Reder RF: Nitrate tolerance: Do "critical" trough plasma levels exist to prevent tolerance? *Circulation* 80:11-215, 1989.
31. Reder RF: Relationship of dose to antihypertensive response of verapamil sustained release. *Clin Res Vol 37, No. 3, p 855A, 1989.*
32. Reder RF: Relationship of dose to antihypertensive response of verapamil-sustained release (V-SR). *J Clin Pharmacol* 29:833, 1989.
33. Hernandez M, Reder R, Marinchak RA, Rials SJ, Kowey PR: A literature-based meta-analysis of propafenone for malignant ventricular arrhythmia. *Clin Res Vol 38, No 3, p 782A, Oct 1990.*

Abstracts (continued)

34. Reder R, Fitzmartin R, Citron M, Spaulding M: Interchangability of various dosage strengths of controlled-release morphine (MS Contin®) in patients with cancer related pain. *Proceedings of ASCO Vol. 12:448, 1993.*
35. Levy MH, Fitzmartin R, Reder R: Comparison of immediate versus controlled release morphine (MS Contin) in the long term management of cancer related pain. *Proceedings of ASCO Vol. 12:455, 1993.*
36. Bouchard J, Reder R, Slagle S, Kaiko R, Cronin C, Goldwater D, Solomon D: Factors in conversion of cancer patients from oral analgesia to patient controlled analgesia (PCA) devices. *Proceedings of ASCO Vol. 12:459, 1993.*
37. Glajchen M, Blum D, Fitzmartin R, Reder R: Clinical guidelines for oncologist-patient communication in cancer pain management. *Proceedings of ASCO Vol. 12:459, 1993.*
38. Lazarus H, Reder R, Slywka J, Tan C, Fitzmartin R: Survey of clinical experience with controlled-release morphine (MS Contin®) in cancer patients. *Proceedings of ASCO Vol. 12:466, 1993.*
39. Reder RF, Kaiko R, Wright C: Association of onset of typical opiate side effects with plasma morphine concentrations. *Proceedings of College on Problems of Drug Dependence, Inc., Fifty-fifth Annual Scientific Meeting, June 12-17, 1993.*
40. Kaiko RF, Reder RF, Grandy RP, Fitzmartin RD, Goldenheim PD: Controlled-release oral morphine (MS Contin tablets, MSC) for postburn analgesia in adult and pediatric patients. *Proceedings of International Association for the Study of Pain, 7th World Congress on Pain, August 21-27, 1993, p. 312.*
41. Reder RF, Kaiko R, Kisicki J: The relationship of plasma morphine concentrations to typical opiate side effects in normal volunteers when oral morphine is administered with and without naltrexone. *Proceedings of International Association for the Study of Pain, 7th World Congress on Pain, August 21-27, 1993, p. 535.*
42. Glajchen, Blum, Fitzmartin, Reder: Non-medical aspects of cancer pain relief: Converting obstacles into practice interventions. *American Pain Society, Orlando, Florida, November 4-7, 1993, p. A-78.*
43. Glajchen, Blum, Calder, Fitzmartin, Reder: Refining a role for social work within the multi-disciplinary pain team. *American Pain Society, Orlando, Florida, November 4-7, 1993, p. A-79.*
44. Cooper, SA, Witte, JF, Mooar, PA, Fitzmartin, RD, Slywka, J, Reder, RF, Kaiko, RF, Grandy, R: Comparison of analgesic potency and safety of two controlled-release oral morphine tablets in orthopedic post-surgical pain. *American Pain Society, Orlando, Florida, November 4-7, 1993, p. A-85.*
45. Baker, DK, Buckley, BJ, Reder, RF, Tan, CT: Reduction of cancer related pain in children using controlled release morphine. *Third International Symposium on Pediatric Pain, Philadelphia, PA, June 8, 1994.*
46. Grandy R, Reder R, Fitzmartin R, Benziger D, Kaiko R: Steady-State pharmacokinetic comparison of controlled release oxycodone (OxyContin™) tablets vs. oxycodone oral liquid. *Journal Clin Pharmacol; Vol. 34:1015, October 1994.*
47. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski: Pharmacokinetic model for a new oral controlled release formulation of oxycodone. *Anesthesiology, Vol 81, No. 3A, September, 1994.*
48. Benziger DP, Thomas G, Miotto J, Grandy R, Kaiko R, Reder R: Bioavailability and pharmacokinetics of controlled-release oxycodone (OxyContin) tablets vs. oxycodone oral liquid. *American Pain Society Program Book, 1994; A-121, #94732.*

Abstracts (continued)

49. Kaiko R, Grandy R, Benziger D, Oshlack B, Fitzmartin R, Thomas G, Reder R, Goldenheim P:PK/PD relationships of controlled-release oxycodone and metabolites in normal volunteers. *American Pain Society Program Book, 1994:A-123, #94736.*
50. Reder R, Kaiko R, Grandy R, Fitzmartin R, Bashaw D:Steady-state bioavailability comparison of controlled release oxycodone (OxyContin) tablets vs. oxycodone oral liquid. *American Pain Society Program Book, 1994:A-35, #94604.*
51. Roth S, Burch F, Fleischmann R, Iwan T, Fitzmartin R, Kaiko R, Benzigner D, Reder R, Lacouture P: PK/PD relationships in patients receiving controlled-released (CR) oxycodone. *Clinical Pharmacology & Therapeutics, Vol. 57(2):165, February, 1995.*
52. Lacouture PG, Iwan T, Fitzmartin R, Kaiko R, Benziger D, Reder R, Goldenheim P:PK/PD relationships in patients receiving controlled-release (CR) oxycodone. *1st Scientific Meeting of the European Federation of IASP Chapters, 5/18-21, 1995.*
53. Reder R, Grandy R, Lacouture PG, Fitzmartin R, Kaiko R:PK/PD relationships in normals and patients. *College on Problems of Drug Dependence, June 1995.*
54. Benziger DP, Levy SA, Fitzmartin RD, Reder RF:Dose proportionality of 10, 20 and 40 mg controlled-release oxycodone hydrochloride tablets (OxyContin™). *American College of Clinical Pharmacy, Washington, DC, August 8-9, 1995. Pharmacotherapy 1995; 15(3):391, #188.*
55. Kaplan R, Parris W, Croghan M, Citron M, Herbst L, Rosenbluth R, Slagle S, Buckley B, Reder R:Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (Oxycr) in cancer pain patients, *American Pain Society 14th Annual Scientific Meeting, Los Angeles, CA, p. A-146 (Abst. #95882) Program Book, November 9-12, 1995.*
56. Reder RF, Fitzmartin RD:Physician survey of attitudes about controlled-release oxycodone (Oxycr), *American Pain Society 14th Annual Scientific Meeting, Los Angeles, CA, p. A-144 (Abst. #95878) Program Book, November 9-12, 1995.*
57. Grandy R, Fitzmartin RD, Kaiko R, Reder R, Benziger D:Pharmacokinetics and pharmacodynamics of controlled-release oxycodone (OxyContin™) in healthy elderly and young adult volunteers, *American Pain Society 14th Annual Scientific Meeting, Los Angeles, CA, p. A-145 (Abst. # 95880) Program Book, November 9-12, 1995.*
58. Benziger DP, Kaiko R, Fitzmartin R, Reder R:Bioequivalency and pharmacokinetics of controlled-release oxycodone tablets (OxyContin™), *American Pain Society 14th Annual Scientific Meeting, Los Angeles, CA, p A-145 (Abst. #95879) Program Book, November 9-12, 1995.*
59. Fitzmartin RD, Reder RF: Stigma associated with opioid therapy for pain: results of a health care provider survey, *American Pain Society 14th Annual Scientific Meeting, Los Angeles, CA, p. A-144 (Abst. #95887) Program Book, November 9-12, 1995.*
60. Reder RF, Grandy RP, Lacouture PG, Fitzmartin RD, Kaiko, RF: Oxycodone Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships in Normals and Patients, *NIDA Research Monograph 162, 1996, p. 273.*

Abstracts (continued)

61. Kaplan R, Parris WCV, Citron ML, Zhukovsky DS, Khojasteh A, Buckley BJ, Tan C, Reder, RF, Kaiko, RF: Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain, a double-blind study, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 58, p. 20.*
62. Parris WCV, Johnson BW Jr., Croghan MK, Moore MR, Khojasteh A, Reder RF, Slagle NS, Buckley BJ: Therapeutic evaluation of controlled-release oxycodone (OxyContin™) tablets in the treatment of chronic cancer pain: a double-blind study, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 59, p. 20.*
63. Citron ML, Croghan MK, Parris WCV, Buckley BJ, Slagle NS, Reder R: Use of rescue analgesic for breakthrough pain in chronic cancer patients, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 60, p. 21.*
64. Berger A, Holme C, Saberski, L, Zelterman D, Davis LE, Tan C, Reder R: Controlled-release oral morphine (MS Contin® Tablets) versus fentanyl transdermal system (Duragesic®) for the outpatient treatment of cancer pain, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 61, p. 21.*
65. Narcessian EJ, Clark G, Reder RF: Validation study of the controlled-release oxycodone (OxyContin™) tablet package insert prior to FDA approval for marketing, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 170, p. 53.*
66. Reder R, Lacouture P, Kaiko R, Fitzmartin R, Goldenheim P, Salzman R, Roberts M: Ease of titration to stable pain control in chronic pain patients with controlled-release oral oxycodone (OxyContin™) tablets, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 171, p. 53.*
67. Goldenheim P, Ingber E, Reder R, Fitzmartin R, Benziger D, Cheng C, Andrews J, Kaiko R: Predictability and consistency of peak (P) and trough (T) plasma oxycodone with different doses and patient populations after q6h oxycodone (IR) and q12h OxyContin™ tablets (CR), *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 226, p. 286.*
68. Fitzmartin R, Iwan T, Lacouture PG, Reder R, Kaiko R: Safety of controlled-release (CR) oxycodone (OxyContin™ tablets) in elderly patients: a meta-analysis, *8th World Congress on Pain Meeting, August 17-22, 1996, Vancouver, British Columbia, Canada, 276, p. 519.*
69. Reder R, Lockhart E, Shi M: A comparison of the duration of adverse drug effects (ADEs) associated with controlled-release oxycodone (OxyContin™) and immediate-release oxycodone (IR), *15th Annual Scientific Session, American Pain Society, November 14-17, 1996, p. A-66.*
70. LoRusso P, Berman B, Silberstein P, Mullane M, Citron M, Weinstein S, Reder R, Smith M, Buckley B, Shi M: Comparison of controlled-release oxycodone (OxyContin™) tablets to controlled-release morphine (MS Contin®) in patients with cancer pain, *15th Annual Scientific Session, American Pain Society, November 14-17, 1996, p. A-67.*
71. Reder R, Buckley B, Shi M. Use of the FACT-G in the Comparison of OxyContin® to MS Contin® Tablets in the treatment of cancer pain., *3rd Annual Meeting, American Academy of Pharmaceutical Physicians, December 8-10, 1996.*

Abstracts (continued)

72. Stambaugh JE, Reder RF, Stambaugh M, Davis M: Double-Blind, Randomized, Two-Period Crossover Efficacy and Pharmacokinetic Comparison of Immediate-Release Oxycodone (IR) and Controlled-Release Oxycodone (CR) in Cancer Patients with Pain. *Clin Pharmacol Ther* 1997; 61(2): 197.
73. Weinstein S, Lo Russo P, Berman B, Silberstein P, Mullane M, Citron M and Reder R. Controlled-release oral oxycodone (Oxycontin®) compared to controlled-release morphine (MS Contin®) in patients with cancer pain. *Fifth Congress of the European Association for Palliative Care; 10-13, September 1997, London S30-S31.*
74. Reder RF, Stambaugh JE, Stambaugh M and Davis M.: Double-Blind, Randomized, Two-Period Crossover Efficacy and Pharmacokinetic Comparison of Immediate-Release Oxycodone (IR) and Controlled-Release Oxycodone (CR) in Cancer Patients with Pain *Fifth Congress of the European Association for Palliative Care; 10-13 September 1997, London S31.*
75. Kaiko R, Lockhart E, Grandy R, Reder R. Bioequivalency of an 80 mg Controlled-Release Oxycodone (OxyContin®) Tablet compared to two 40 mg CR Oxycodone Tablets. *Fifth Congress of the European Association for Palliative Care; 10-13, September 1997, London S33.*
76. Reder, RF, Kaiko RF, Lockhart E, Benziger D, Slagle S, Goldenheim P. Controlled-Release Oral Oxycodone (OxyContin®) Tablets for the Control of Cancer Pain. *II Congress of the European Federation of IASP Chapters (EFIC) 23-27 September 1997, Barcelona, Spain. p. 365*
77. Reder R, Shi M, Lockhart E, Kaiko R. Oxycodone may be Associated with a Lower Incidence of Hallucinations than Morphine. *II Congress of the European Federation of IASP Chapters (EFIC) 23-27 September 1997, Barcelona, Spain. p. 366.*
78. Reder, R, Shi, M., Kaiko, R. Relationship Between Pain Intensity Scores Captured on a Categorical Scale (CAT) Compared to Those on a Visual Analogue Scale (VAS). *16th Annual Scientific Meeting American Pain Society 23-26 October 1997, New Orleans, LA, p. 121.*
79. Reder, RF, Buckley, B. Open Label Clinical Use Study of Controlled-Release (CR) Oxycodone Tablets (OxyContin) Administered Orally Every 12 hours for the Management of Pain. *17th Annual Scientific Meeting American Pain Society 5-8 November 1998, San Diego, CA, p. 129.*
80. LoRusso, P., Reder, RF, Buckley, B, Shi, Ming Gao. The Effects of Oral Controlled-Release Morphine and Oxycodone on Cancer-Related Neuropathic Pain. *17th Annual Scientific Meeting American Pain Society 5-8 November 1998, San Diego, CA, p. 130.*
81. Buckley, B, Reder, RF. Controlled-Release (CR) Oxycodone Tablets (OxyContin) Administered Orally Every 12 Hours: Patients with Neuropathic Pain. *17th Annual Scientific Meeting American Pain Society 5-8 November 1998, San Diego, CA, p. 130.*

Symposia

1. Evolving Technologies for Expecting the Drug Development Process, *Drug Information Association, June 11, 1996.*
2. Wright C, Citron M, Portenoy R, Reder R: Breakthrough pain: prevalence, characteristics and new treatment strategies, *15th Annual Scientific Session, American Pain Society, November 16, 1996.*