

Drug Injury

Liability, Analysis and Prevention

Second Edition

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web site: www.lawyersandjudges.com
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Library of Congress Cataloging-in-Publication Information

O'Donnell, James, Pharm. D.

Drug injury : liability, analysis, and prevention / James T. O'Donnell; contributing authors, Loyd V. Allen ... [et al.].

p. cm.

Includes bibliographical references and index

ISBN 1-930056-04-4

1. Products liability--Drugs--United States. 2. Drugs--Law and legislation--United States. 3. Trial practice--United States. I. Allen, Loyd V. II. Title

KF1297.D7 O36 2000

346.7303'8 21--dc21

00-032251

ISBN 1-930056-04-4

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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Preface

Drug Injury, Second Edition was designed to serve as a reference for attorneys, pharmacists, physicians, risk managers, nurses, drug manufacturers, and regulators—as well as anyone with any interest in drug use and drug injury. It summarizes the FDA’s responsibility in monitoring drug safety. It reviews drug-product-related liability issues that focus on the manufacturer’s role in providing for drug safety. The book identifies important roles that pharmacists play in enhancing medication safety and effectiveness, and demonstrates what can happen when pharmacists do not function adequately. By focusing on the most dangerous drugs, the reader can learn from the tragedies and mistakes of others, look at their own practice settings, and avoid making similar mistakes.

The second edition contains forty-eight chapters, ten of which were contributed by lawyers, including those who practice at the FDA, in healthcare, regulatory law, malpractice defense, and the prosecution of product liability. The remaining thirty-eight chapters were contributed by accomplished physicians, pharmacologists, pharmacists, nurses, and other scientists, in three areas of focus:

1. How are drugs developed?
2. What drugs cause the most injury?
3. What can clinicians and health systems do to minimize risk and improve drug safety?

With rare exception, all of the chapters are either new or extensively revised since the release of the first edition of this book. The two chapters that have not been updated contain information that remains timely. The Omniflox and Vaccine Litigation chapters have been deleted, since these topics have become dated. Chapters new to the Second Edition include Drugs for Asthma, Allergies, and Anaphylaxis: Harm from Use, Misuse and Non-Use, by Constantine John Falliers, MD, an eminent allergist; and Drug Induced Neph-

rotoxicity, by nephrologists Sica and Gehr. Attorney Kip Petroff has also contributed two new chapters, including Dangers at the Drug Store: Practical Comments about the Pondimin and Redux Litigation, which completes the story of the diet pill Redux, as described in the First Edition by Restaino and O’Donnell. Petroff is recognized as a pioneer and legal authority in diet-drug litigation. Petroff’s second new contribution, The Failed System of Drug Warnings in America, was written about a year ago, and is prophetic! Both the lay and trade presses are full of commentary and concerns about the Vioxx withdrawal. A Senate Committee hearing has since been held, with testimony from an FDA drug-safety officer that Vioxx and several other best-selling drugs were somehow not adequately tested, monitored, and warned. (More about Vioxx later!)

Chapters on the Pharmaceutical Industry, the FDA, and The Dietary Supplement Act have been updated for this edition. Additional chapters in this subject area include FDA Regulation of Clinical Investigations by Walters, a former FDA inspector; and Protection of Subjects in Clinical Research, by Clark and Ahuja. Dr. Clark has described himself as the “research police,” and his review of requirements for clinical research will provide a thorough and up-to-date reference on the subject.

Chapters on ephedra, Rezulin, Baycol, E-Ferol, and blood-factor products reflect the latest news on these drug products, which have played large roles in drug-product liability and represent some very interesting theories of liability. Since the analysis of drug injury can help prevent recurrence by educating the entire healthcare profession, this book presents numerous case reports. Of interest, despite FDA’s recognition of ephedra/caffeine dietary supplements in 1995 and a proposed rule to limit use and dosage, it still took the agency until 2004 to finally and officially ban the useless (and obviously dangerous) product. Up until this point, ephedra had been regulated as a “dietary supplement.”

In reality, this substance acted like a toxic drug. Finally, there is a peek at Oxycontin litigation in the form of a report by this expert, as part of an updated chapter on Pain Medications.

Many chapters—such as Performance Enhancing Drugs—address toxic drug products, such as anabolic steroids, modified steroids, corticosteroids, hepatotoxins, diabetic drugs, and others. Some of these chapters include discussions and case reports on drug-product liability issues related to the individual drugs.

I believe that the pharmacist's most important job is to ensure that drugs are used safely and effectively. We included updated chapters on many of the specialized pharmacist chapters from the First Edition, and have recruited contributions in the areas of emergency-department care, the identification of drug dosage forms, the appropriate use of intravenous medications, the role of the pharmacoepidemiologist, and a new chapter on pharmacist errors. A special chapter by attorney Sweeney discusses the roles of pharmacy technicians. Del Konnor, a former Executive Director of the Managed Care Pharmacy Association, has contributed a chapter on pharmacy-benefits managers (PBMs), who currently affect millions of American lives, and who also have been involved in some high-profile litigation. We are fortunate to have a compiled Pharmacy Case-Law Update by Morris and Carpenter—both pharmacist/attorneys—adapted from a very popular presentation at the Annual Meeting of the American Society of Pharmacy Law.

Pharmacy got a big black eye, dropping a notch in the public trust, following the news of the Courtney case—the Kansas City pharmacist who was diluting chemotherapy drugs and cheating patients out of life-sustaining (or at least palliative) chemotherapy. This was not malpractice—more like greed-driven criminal acts. A special review of the Courtney story is included in a new chapter on Pharmacist Malpractice.

A chapter by medical-malpractice defense attorneys Barkus and Derian covers physician and hospital liability in drug and medical-device litigation. The medication error chapter has been extensively expanded. A collaboration amongst pharmacist O'Donnell, nurse Iyer, and physician Cohen brings three different analyses and points of view to this topic exploration. According to the Institute of Medicine's (IOM) report "To Err is Human," originally published in 1999, between 44,000 and 98,000 people die every year from medical errors that occur in hospitals. About 7,000 of these were attributable to medication errors in 1993—comprising one out of every 131 outpatient deaths and one out of every 854 inpatient deaths. One study referenced in the report found that almost two percent of all hospital ad-

missions experienced a preventable adverse drug event, resulting in average increased hospital costs of \$4,700 per admission, or about \$2.8 million annually for a 700-bed teaching hospital. This problem is not limited to hospital patients either. In fact, hospitalized patients represent only a small number out of the total population at risk of experiencing a medication-related error. "Numerous studies document errors in prescribing medications, dispensing by pharmacists, and unintentional non-adherence on the part of the patient," reads the IOM report. "Medication errors have the potential to increase as a major contributor to avoidable morbidity and mortality as new medications are introduced for a wider range of indications." A *JAMA* article described the enormity of drug-related deaths as the equivalent of two 747s crashing every week. Of course, where there is injury, there may be litigation. When education and safe-pharmacy practice fail, affected patients have a right to investigate and seek damages for their injuries. Many times, that is all that they can do, because their injuries are permanent or fatal.

Because drugs are ubiquitous, and because they affect people's lives and practice outside the walls of the hospital and drugstore, we again include chapters on Recreational Drugs and the Forensic Pharmacist. We have also added a new chapter on Drug Testing in the Workplace, by Anne D. ImObersteg, a toxicologist/attorney. As stated earlier, a focused audience is attorneys, who usually have no training in FDA, pharmacy, or regulatory law, and who certainly have no training in pharmacology or the pathology of drugs. Yet, in a wide spectrum of practices, attorneys must master these complex topics to represent their clients. The First Edition of *Drug Injury* was well received by legal, medical, pharmacy, and nursing practitioners and scholars. The First Edition is used as a textbook in several universities, and can be found in numerous medical, pharmacy, and law libraries, the FDA library, and in private law offices throughout the United States.

And, finally . . . Vioxx.

The only good thing about a delayed publication of this book is that the Vioxx withdrawal and some of its immediate fallout occurred before the final press date. As mentioned above, there has already been a Senate hearing on the topic, looking for answers on how this drug got to and stayed on the market with such serious toxicity. A short summary of the events to date gives a little bit of the story: Merck announced a market withdrawal of their \$3 billion blockbuster drug, Vioxx, on September 29, 2004. The cardiovascular risk (heart attacks, blood clots, strokes) that had dominated the medical news for the prior three years was proven again in a second study. Merck stock price dropped 25% in one day, a \$25 billion drop in the capitalization of the company.

Patients, physicians, pharmacists, the news media, the FDA—everyone had comments and concerns. Questions were raised about a “class effect”—did this toxicity extend to other “COX-2 inhibitors,” such as Celebrex (Pharmacia) or Bextra (Pfizer)? Lots of questions. Overnight, amidst Internet and television solicitations by attorneys recruiting Vioxx cases, Merck announced that there were several hundred lawsuits filed. Recently, Merrill Lynch estimated an \$18 billion litigation price tag related to Vioxx.

Vioxx is another shocking and disturbing chapter in the pharmaceutical industry. Shocking because it scares patients who take prescription medications, and it disheartens physicians and pharmacists who prescribe and dispense the drugs. Since the publication of the First Edition, several other drugs have been removed from the market for safety reasons, and severe prescribing limitations have been applied to many more.

A review of the pharmacology of Vioxx may answer some questions as to what happened. Aspirin (acetylsalicylic acid) has been in use for over one hundred years and it has had great success in relieving the pain and inflammation caused by arthritis. For several centuries prior to the chemical synthesis of acetylsalicylic acid, ground willow bark was used to relieve fever, pain, and inflammation. The willow bark worked because it contained salicylic acid. Even after it was chemically described, the mechanism of action of aspirin remained a mystery until about thirty years ago, when Sir John Vane described the chemical pathways of prostaglandin synthesis. The process identified prostaglandins. Prostaglandins are found throughout the body and serve as mediators of cell-membrane function and other physiological functions. Of course, we know that more than a dozen NSAIDs (non-steroidal anti-inflammatory drugs) were developed in the intervening 30 years. These NSAIDs worked on this prostaglandin cascade.

Two sites of possible drug action were discovered, both of which featured an enzyme called cyclooxygenase (COX). These two sites of biological synthesis of prostaglandins are called COX 1 and COX 2. COX 1 is thought to be a site used to protect cells and cell membranes, while COX 2 is thought to activate components of the body’s inflammatory cell response to injury or infection. Prostaglandins can promote vasodilation, change capillary permeability, and modulate the degree and extent of inflammation. In conditions such as rheumatoid arthritis (RA), inflammation is accompanied by pain, swelling, and fever.

Aspirin is a member of the family of NSAIDs, which include Motrin, Advil, Butazolidin, Naprosyn (Aleve), Voltaren, Clinoril, and Indocin. All of these NSAIDs are effective and similar in effectiveness at therapeutic doses. All

of them also have the potential for GI side effects, especially gastric ulcers and GI bleeding. All of the listed NSAIDs inhibit both COX 1 and COX 2, and because both COX 1 and COX 2 are found throughout the body, they have other influences that are still being discovered. One such function is that inhibition of COX 1 receptors interferes with the amount and thickness of the mucosal lining of the stomach, which results in gastric acid coming into contact with the underlying tissue with bleeding and ulcer formation. Another effect of COX-1 inhibition is an effect on platelets that renders them less “sticky,” and therefore reduces their ability to form the platelet plugs that initiate thrombosis inside a blood vessel. It is now understood that in patients at risk for cardiovascular heart disease, it is a good thing for platelets to be less likely to aggregate (this diminishes the risk of coronary-artery thrombosis in arteries with damaged intimal linings due to atherosclerosis).

Vioxx was developed in response to the NSAIDs predictable risk of GI bleeding in the event of simultaneous COX-1 and COX-2 inhibition. If a chemical could be found that selectively inhibited only COX 2 and had little or no effect on COX 1, patients who had not been able to tolerate NSAIDs would be able to obtain relief from pain and inflammation, without the GI side-effect risks. Vioxx is considered to be a specific COX-2 inhibitor.

Vioxx is no more effective than non-specific NSAIDs in inhibiting inflammation. The manufacturer’s claims and promotion of this product are based on the lack of adverse effect of Vioxx on the gastric mucosa. Researchers have hypothesized that there is more than one iso-enzyme form for COX 2. One iso-form of COX 2 might be associated with disease states, such as RA, and another iso-form of COX 2 might be involved with normal physiology.

COX-1 inhibition affects the following parts of the body: synovial joint tissue, platelet aggregation, gastric mucosa, and the kidneys. COX-2 inhibition affects the following body tissues and/or functions: synovial joint tissue, vascular endothelium, tissue repair, bone formation, and the kidneys.

Platelets are affected by non-selective COX-1 and COX-2 inhibitors, by reducing platelet production of thromboxane, A₂ (TXA₂). This product is part of the cascade of chemical reactions that the body uses to begin and limit coagulation in normal physiology. Non-selective NSAIDs, such as aspirin, slightly diminish the “stickiness” of platelets, which are literally physiological plugs. The effect is a slight degree of anti-coagulation, which is desirable in patients at risk for a coronary-artery thrombosis. With selective COX-2 inhibition, platelet agglutination increases (or, at least, does not provide the anti-coagulation benefit of non-

selective NSAIDs). Selective COX-2 inhibition, as seen with celecoxib, elevates blood pressure and promotes leukocyte adherence.

In conducting clinical studies of safety and efficacy, the manufacturer limited its safety data to patients who had received Vioxx for up to nine months. After receiving market approval, this drug was highly promoted, and millions of doses have been taken. Post-marketing data shows that at around eighteen months of Vioxx use, an increased incidence of cardiovascular adverse events was being reported. It was unclear whether this unexpected event is the result of an unexplained risk of Vioxx causing coronary and cerebral artery thrombosis, or whether it could be, instead, due to the lack of platelet inhibition and anti-coagulation provided by non-specific NSAIDs. Merck argued the latter. What is clear is that the adverse events were occurring after the time period employed in the clinical trials. In other words, the clinical trials had not evaluated the risk of these serious adverse effects prior to market release.

It is obvious that nine months was not a long-enough study period to successfully uncover the long-term risks of Vioxx in a population likely to continue to take this or another drug for several years. Secondly, if the increased CV risk is due to a failure to interact with COX 1 while inhibiting COX 2, then this should be considered a class effect, as the increased risk could be shared by other COX-2 inhibitors on the market, such as Celebrex and Bextra.

The FDA's AERS database contains voluntary reports from the population of adverse events reported in association with prescription medications. All of the AERS reports in the database through first quarter, 2002, were examined for the drug names Vioxx, Celebrex, and naproxen. All reports that listed one or more of these drug names were then searched for reports of thrombotic events involving the heart and brain. These data do not establish cause and effect, but they do show that the risk of acute myocardial infarction (almost always due to blockage caused by atherosclerosis and thrombosis) is twice as high with Vioxx than it is with non-selective NSAIDs, such as naproxen.

The populations studied in clinical trials are not a subset of the general population, and, therefore, may not be representative of the risk the population experiences after the release of a newly approved drug to the general prescription-drug market. The continuing influence of COX-2 inhibitors on cardiovascular and cerebrovascular adverse effects will require further study to evaluate the risk exposure faced by the general population. Prospective studies evaluating cardiac outcomes after long-term administration of rofecoxib (or other COX-2 inhibitors) in combination with aspirin have not been conducted. Prospectively designed studies to

collect additional CV outcomes data from the selective COX-2 inhibitors are currently underway. Data from these prospectively designed studies, when added to the extensive data already available, will provide an even more comprehensive picture of the CV safety profile of the selective COX-2 inhibitors.

Summary

In closing, *Drug Injury, Second Edition* is intended to serve as a broad and deep reference for anyone with a professional or personal interest in drug use and the dangers of drug injury. The book shows how pharmacists play pivotal roles in the proper administration and use of prescription medications, and clearly highlights the perils of untrained or careless practitioners. I and all of the authors and editors of *Drug Injury* sincerely hope that readers will learn from the lessons contained within this text, collaborating together to create a safer future for all of us.

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