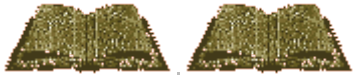
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Book Reviews: Technical Books Section



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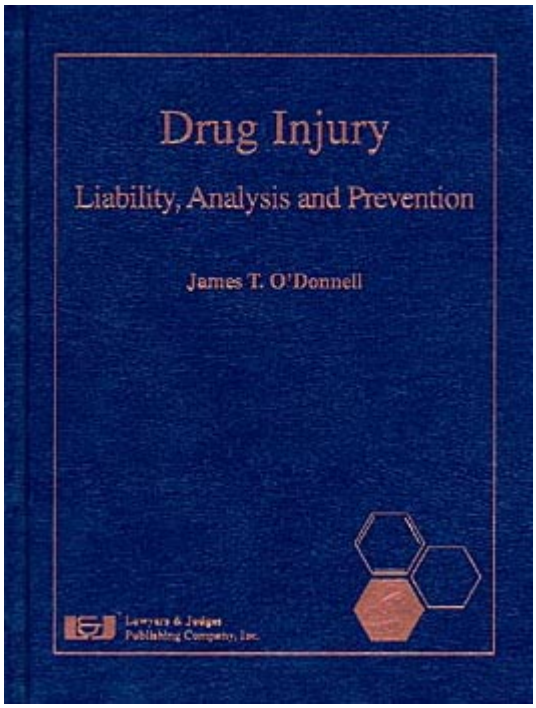
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ESSENTIAL READING FOR LAWYERS AND FORENSIC PHYSICIANS

Drug Injury - Liability, Analysis and Prevention, 2001 *by* James T. O'Donnell, Pharm.D., MS
Lawyers and Judges Publishing Company, Inc., P.O. Box 30040, Tucson, AZ 85751-0040, 696 pages, ISBN 1-930056-04-4. $119.00.

Click cover to buy from Amazon



In the modern world we are surrounded by millions of chemicals, thousands of which qualify as a drug. What is a drug? There are a multitude of proper, scientific definitions, but one wag defined it as a substance which when injected into a rat, will produce a scientific report. Eric Hodgins (1899-1971), US writer and editor, once defined a miracle drug as any drug that will do what the label says it will do! These "fun" definitions, more than anything else underscore people's unconcerned, rather apathetic attitude towards modern drugs. Why is this so?

View this book on Amazon

A number of reasons could be advanced for this. One of the reasons is that several drugs don't give you the intended relief, and many might actually aggravate disease and even result in death. Several such cases have led to prosecutions of manufactures, retailers, nurses, doctors, pharmacists - in fact anyone connected with the chain of delivering the drug to the patient. One of the most illustrative examples of this phenomenon occurred in Germany in 1958 when the drug thalidomide ($C_{13}H_{10}O_4$) caused a number of serious birth defects in children. In Germany, this was touted as a revolutionary new sedative and hypnotic for pregnant mothers. Many mothers took it but many of them gave birth to children with serious birth defects, with attendant medico legal problems. The drug was quickly withdrawn from the market. Luckily the drug never reached more populous nations such as India. One can only imagine the volume of medico legal fallout had this actually happened!

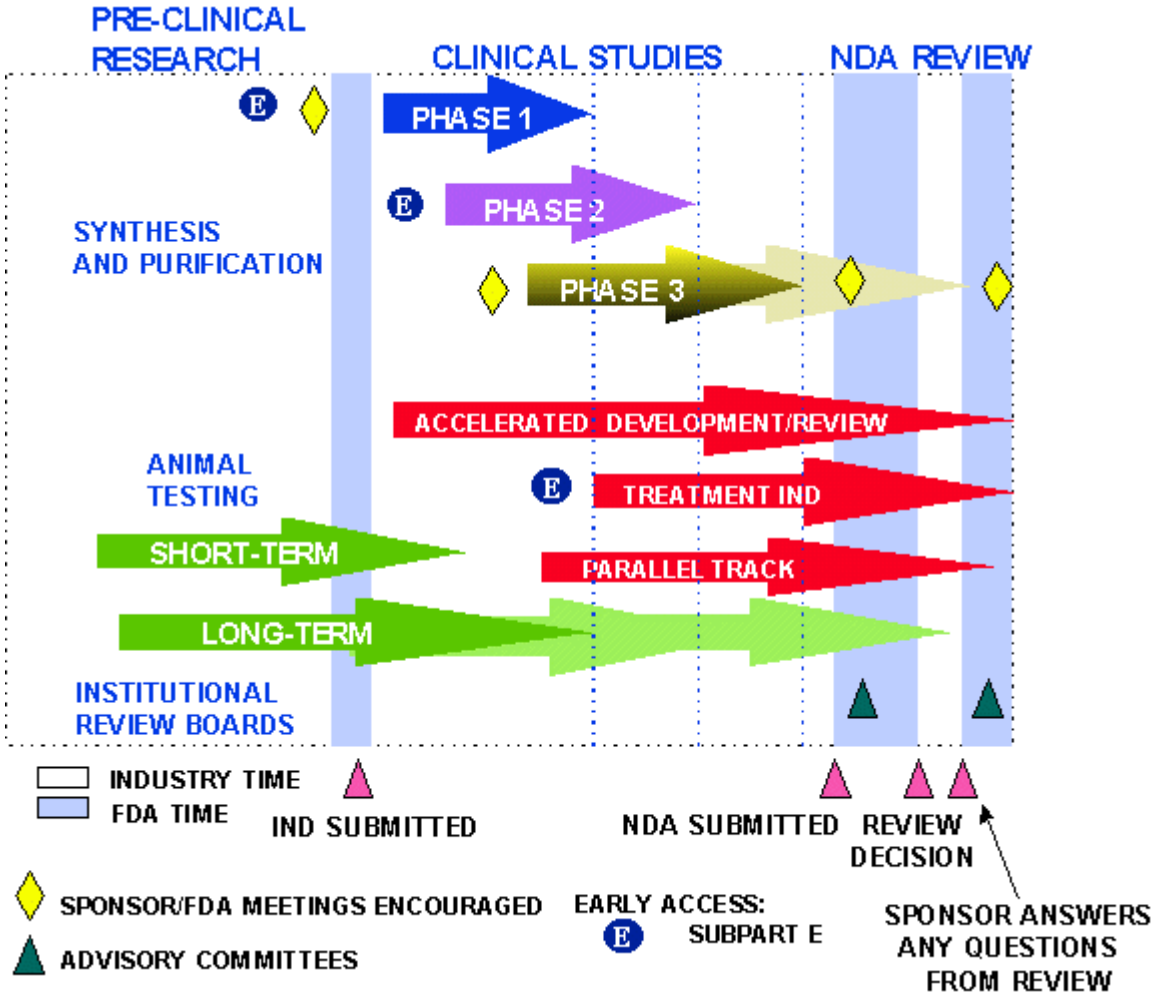
How do the clinician, pharmacists, nurses, and other paramedical staff save themselves from possible litigation arising from drug use? What do they do to safeguard themselves? Well, till now there was no authentic book available to them. The book under review serves this purpose admirably.

The book is divided into three parts, each dealing with one broad area related to drug injury. Part one tells us about the whole pharmaceutical process; part two deals with specific high risk drug therapies which commonly result in injury and litigation and part three deals with issues related to pharmacy malpractice.

Part One

Part one deals with - quite rightly - with the pharmaceutical process itself. How is a drug first conceived by the drug company? How is the proposal put before the Food and Drug Administration (FDA)? How are the field trials done? How is the drug ultimately approved? All these, and several other issues are discussed in detail. These issues are very pertinent for all clinicians and pharmacists to know.

The new drug development process. A Black and White version of this diagram appears on page 5 of this book. Click to enlarge



The New Drug Application (NDA) is actually the starting point of the whole process, as can be seen from the accompanying diagram on the right. This is an application which a drug manufacturer gives to the FDA regarding a new drug which he proposes to launch in the market. Center of Drug Evaluation and Research (CDER) classifies these applications into seven categories, starting from the most innovative (type 1) to the least (type 7).

Type 1 drug is an entirely new molecular entity. Type 2 drug is not a new molecular entity, but a new salt of a previously approved drug. Type 3 drug is neither a new molecular entity, nor a new salt; instead it is a new formulation of a previously approved drug. Type 4 drug is a new combination of two or more drugs. Type 5 drug is actually an already marketed drug product. The only novelty is that the manufacturer is new. Type 6 drug is a drug which is already marketed drug, but for which a new indication has been claimed, i.e. the drug is claimed to be beneficial in a different disease, than it has traditionally been used for. And finally type 7 drug is a drug which is

an already marketed drug product. Review priority of the drug is given by letters A and B. A refers to standard reviews for drugs similar to currently available drugs. B refers to priority reviews for drugs that represent significant advances over existing treatments.

When such applications are given to FDA, the manufacturers actually submit results of non-clinical (animal) trials, and clinical trials, and a host of other information, and on the basis of that information, the application is processed further.

For reader's benefit, the first chapter gives various statutes applicable to drugs and pharmacists in general. Some among them being the *Food and Drug Act of 1906, Federal Food, Drug and Cosmetic Act (1938), Durham-Humphrey Amendment (1951), Drug Amendments of 1962* and *Orphan Drug Act (1983)*. Various relevant provisions of these Acts are summarized. Sample this provision of the Orphan Drug Act (1983). To foster orphan drug development, this law allows the drug companies to take tax deductions for about three-quarters of the cost of their clinical studies (for the uninitiated, "orphan drugs" are drugs and other products for treating rare diseases. They have very little market, and thus offer little or almost no profit to the manufacturer). This is indeed a useful piece of legislation, for if such a law had not been there, no company would really be interested in developing such drugs.

...It was an FDA medical officer Frances O. Kelsey, M.D. who was instrumental in keeping the drug thalidomide off the US market. This news aroused public interest in controlling drugs, and Drug Amendments of 1962 were passed as a result in October 1962. These amendments tightened control over the drugs...

It was an FDA medical officer Frances O. Kelsey, M.D. who was instrumental in keeping the drug thalidomide off the US market. This news aroused public interest in controlling drugs, and *Drug Amendments of 1962* were passed as a result in October 1962. These amendments tightened control over the drugs. As a result of these Amendments, drug companies, now not only had to prove effectiveness, but also safety. Moreover these amendments applied retroactively to 1938, when the FDC Act was passed. Pre-1938 drugs were allowed to be sold without restriction as it was widely perceived that they were safe drugs.

The chapter ends in several interesting and informative appendices (as do several chapters in this book). Appendix A tells us how every one of us can locate correspondence related to drug approval over the internet. The FDA Internet URL is http://www.fda.gov/. The author was asked to investigate the antibiotic Trovan (trovafloxacin). Normally it would have taken lot of paper correspondence, but under the new scenario he could easily retrieve the information via the internet. We are told that Freedom of Information (FOI) office maintains NDA material on their website at http://www.fda.gov/cder/foi/nda/97/020760a.htm.

Appendix B discusses various labeling changes. Appendix C is quite useful, and it discussed an interesting example of FDA action. Roche Laboratories of Nutley, NJ introduced a drug Posicor (mibefradil) in the market in August 1997. It is a calcium channel blocker and was said to be beneficial in the treatment of patients with hypertension and chronic stable angina. At the time it was introduced in the market, it was known that this drug inhibits certain liver enzymes, which are useful in the detoxification of certain other drugs. Three drugs were known at that time. They were astemizole, cisapride and terfenadine. This meant that if Posicor was administered along with any of these drugs, they could accumulate to dangerous levels within the patient's body. This was adequately put over the label. Soon it was found that two other drugs could accumulate, and soon

the number of such drugs grew to 25! Since Posicor offered no definite advantage over other antihypertensive and anti-anginal drugs, it was decided that the risk it posed was quite unreasonable. And finally as a result of FDA action this drug was taken off the market.

Appendix E gives some other useful information, not the least important of which are the FDA hotlines for consumers. Because of the increased public interest, the FDA has established a general toll-free number. Several other hotlines are given in this appendix. But this appendix also tells us that not all information can be given by FDA officials to the general public. In a special sub-heading "Our lips are sealed", the author tells us that in several cases information can not be imparted to the public. For instance FDA employees cannot release any information on unapproved drugs unless the manufacturer has given the agency permission or has already released the information to the public.

Topics covered in "*Drug Injury-Liability, Analysis and Prvention*"

- The Food and Drug Administration (FDA) and the drug approval process
- Dietary supplements
- The pharmaceutical industry
- Clinical research
- Adverse drug reactions and causality assessment
- Diet drugs, redux and FenPhen--two points of view
- Risk benefit analysis: vaccine litigation
- Antidepressants: clinical use and litigation
- The physician and hospital as potential defendants in drug product and medical device claims
- Omniflox
- Theophylline: the unpredictable toxic asthma drug
- Protective orders: safeguarding trade secrets or defense dirty tactics
- Corticosteroids
- Adverse effects of diabetic drugs
- Drug Induced hepatoxicity
- Drug Induced movement disorders
- Analgesic drugs
- Accutane toxicity: focus on suicide
- Performance enhancing drugs: anabolic steroids and dietary supplements/ephedrine
- Recreational drugs
- Regulation of pharmacy practice
- Specialized services
- Nursing home pharmacy
- Pharmacy compounding regulations
- The forensic pharmacist
- Forensic drug testing
- Managed care
- Medication errors
- Mistakes pharmacists make and why
- Taking the pharmacist malpractice case to trial

Chapter 2 is on The Dietary Supplement and Health Education Act of 1994 (DSHEA) and related FDA activities. To begin with, what is a dietary supplement? Several definitions exist, but DSHEA's definition includes herbs or similar nutritional substances, vitamins, minerals, botanicals, and other plant-derived substances, amino acids and concentrates, metabolites, constituents and extracts of these substances. As a result of this definition, such substances as ginseng, enzymes, glandulars, fish oils, and mixtures of these would fall under the heading "dietary supplements". The interesting thing is that the FDA does not authorize or test dietary supplements.

DSHEA was signed by President Clinton on October 25, 1994. A full overview of DSHEA is given in this chapter. Among other things, DSHEA created an Office of Dietary Supplements in the National Institute of Health to coordinate research on dietary supplements, and required the formation of an executive level Commission on Dietary Supplement Labels to report on the use of claims in dietary supplement labeling. Other things discussed in this chapter include, the FDA's role in implementing DSHEA, the boundaries of regulatory classification, labeling of dietary supplements, and claims permitted under DSHEA.

Part Two

This reviewer found Part Two of the book the "juiciest" of all parts. It deals with the high-risk drug therapies, which may actually result in injury and litigation. The first chapter of this part (chapter 5 of the book) quite appropriately deals with Adverse Drug Reactions (ADRs) which are so ubiquitous. We are told that the incidence of adverse drug reactions could be as high as 28%, but in most studies, the figures lie somewhere between 10% and 20%. An incidence of 1 in 200 or greater is considered a high incidence of adverse reaction, and one of 1 in 10,000 or less as low, with others intermediate. High incidence adverse reactions can actually be identified at the clinical trial stage itself, the reason being that at this stage data on about 1000 patients is available, and if the drug has a high incidence of adverse reactions (greater than one in 200), at lease five patients would suffer from these. Adverse reactions with an intermediate frequency can be identified in post marketing surveillance schemes. Low frequency adverse drug reactions can only be verified in case-control studies.

How does the FDA come to know of ADRs? Well, currently there is a voluntary reporting system, whereby physicians and pharmacists report ADRs to the FDA via the Drug Experience Report Form. Since 1962, it is mandatory for all drug companies to report ADRs too. Currently FDA receives about 60,000 reports of ADRs per year, most of which are filed by the drug companies.

The chapter discusses a very important and interesting Catch-22 situation in which FDA often finds itself. Drug companies often blame the FDA for taking too long a time to approve a drug. They claim that FDA keeps sitting over the files and keeps looking for ADRs which are simply not there. On the contrary, several public interest groups claim that the FDA approves the drugs too fast, without taking all the pros and cons into account. An interesting example is given.

...The General Accounting Office (GAO), an investigative agency of the Congress, reviewed all 198 drugs that were approved from 1976 to 1985 and subsequently marketed for a substantial period. The Agency found that out of these drugs 102 had side effects serious enough to warrant either a complete withdrawal from the market or major changes in labels to account for new dangers...

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The Agency found that out of these drugs 102 had side effects serious enough to warrant either a complete withdrawal from the market or major changes in labels to account for new dangers. This comes to a staggering figure of 52%! Naturally officials of the FDA reacted very angrily to GAO. Dr. Robert Temple, Chief of Drug Evaluation for the FDA, called it "the worst piece of stuff ever to come out of there". The reader might want to read the full controversy from the book itself.

We are informed that despite the fact the doctors are required to report the ADRs to the FDA, they fail to do so because of the seven so called "deadly sins". Some of these are (i) Complacency - most drugs are believing that only safe drugs are allowed in the market (ii) fear of involvement in litigation (iii) Ambition to collect and publish a personal series of cases, and so on.

Other areas dealt with in this chapter are the various categories of ADRs, drugs which are most dangerous, Identification of the Adverse Drug Reactions, Degrees of Certainty in Drug Causation Analysis and the assessment of adverse drug reactions. Then there are large sections on Adverse reactions manifest in the skin, drug induced hepatic injury, and so on. Readers may enjoy the "Seven Pillars of Foolishness", an interesting section in the same chapter.

We all know that Fenfluramine, dexfenfluramine and phentermine are appetite suppressants which had each been individually approved by the FDA at various points in time. In 1995, the use of these drugs increased enormously following some interesting discoveries by a researcher Michael Weintraub, M.D. Essentially what he found was that the drowsiness often produced by fenfluramine could be cancelled out by the stimulation caused by phentermine. So if these two drugs could be taken in conjunction, the side-effects would cancel out. But very soon problems started surfacing. On September 15, 1997, the FDA requested the withdrawal of both fenfluramine and dexfenfluramine from the market. The reason? In August 28, 1997 issue of the *New England Journal of Medicine*, reports appeared which associated these two drugs with primary pulmonary hypertension.

...Believe it or not, litigation has been associated with such benign sounding activities as vaccination too. Vaccines have been known to cause seizures, brain damages, death and other reactions. In fact, some vaccines such as polio vaccine can cause the disease itself....Chapter 7 deals with litigations related to vaccines...

What's important is that since their removal there have been thousands of lawsuits alleging cardiac valvulopathy, pulmonary hypertension, neurotoxicity, or other conditions such as cerebral vascular accidents and myocardial infarctions as a result of using these drugs. The federal litigation was coordinated into a multidistrict litigation (MDL), overseen by the Judge Louis Bechtle of the Eastern District of Pennsylvania. Details of this interesting controversy - and its outcome - can be studied in great detail in Chapters 6A and 6B, entitled "Diet Drugs, Redux and Fen/Phen - Two points of view".

Chapter 7 deals with vaccine litigation. Believe it or not, litigation has been associated with such benign sounding activities as vaccination too. Vaccines have been known to cause seizures, brain damages, death and other reactions. In fact, some vaccines such as polio vaccine can cause the disease itself. Important statutes related to vaccination are discussed such as The National Vaccine Compensation Act. Under this Act damages of upto $250,000 are available in death cases, and the petitioner is entitled to reasonable attorney's fees and other costs. This fees is limited to $30,000 for claims accruing prior to October 1, 1988. Attorney's hourly rate is set on the basis of the Lodestar method.

There is one statute which says that "no person shall be liable for any injury in the administration of a vaccine." But this statute is meant only for vaccine administrators and not for the manufacturers. In fact in one case Flood v. Wyeth, Wyeth, a drug manufacturer tried to invoke this statute to get relief. But this argument was rejected by the court.

So if you happen to be a counsel for a party who has been injured by vaccination, what should you do? The chapter provides ample advice. Among the first things to be done is to seek all prior lawsuits against the manufacturer. This is a very valuable source of evidence to show notice.

...Chapter 8 deals with the litigation associated with the use of antidepressants. Antidepressants are among the most popular drugs among the general public. In fact, the antidepressants Prozac, Zoloft and Paxil are among the top ten selling prescription drugs in the world. Eli Lilly first marketed Prozac in 1987. Since that time, it has been alleged that patients taking this drug have shown increased suicidal tendencies...

Chapter 8 deals with the litigation associated with the use of antidepressants. Antidepressants are among the most popular drugs among the general public. In fact, the antidepressants Prozac, Zoloft and Paxil are among the top ten selling prescription drugs in the world. Eli Lilly first marketed Prozac in 1987. Since that time, it has been alleged that patients taking this drug have shown increased suicidal tendencies. They are also known to perform violent crimes. In fact by the early 1990s, there were a plethora of lawsuits pending against Eli Lilly & Co. The famous rock and roller Del Shannon and Abbie Hoffman were among them. Several case illustrations are given. This reviewer found all of them very interesting. The reader may particularly want to go through *Docken v. Ciba Geigy*, 739 P.2d 591 (Ore.Ct. App. 1987), *Stebbins v. Concord Wrigley Drugs, Inc. et.al.*, Docket No. 88734 (Mich. Ct. App. 1987), *Kirk v. Michael Reese Hospital*, 483 N.E.2d 906 (Ill. App.1 Dist., 1985), rev'd 513 N.E.2d 387 (Ill., 1987), and *Hand v. Krakowski*, 453 N.Y.S.2d 121 (N.Y.App. Div. 1982). And finally there is a discussion of The Omnibus Budget Reconciliation Act (OBRA) which every pharmacist may like to read.

All the rest of the chapters deal with one or the other important drug, and litigations associated with it. Chapter 10 deals with Omniflox, chapter 11 with theophylline, chapter 12 with corticosteroids, chapter 13 with diabetic drugs, chapter 14 with drug induced hepatotoxicity, chapter 15 with drug induced movement disorders, chapter 16 with pain medications, chapter 17 with Accutane, chapter 18 with Performance enhancing substances and chapter 19 with Recreational drugs such as alcohol, cocaine and marijuana. Each chapter is very well researched and has been written by a separate specialist having an expertise in that particular area. Important case studies are given in each chapter related to that particular drug.

Some of these chapters deserve mention. For instance the chapter of theophylline appeared particularly interesting to this reviewer. It is supposed to be the most widely used medication for chronic asthma sufferers, and is used to treat wheezing and other respiratory conditions. It is also used in the treatment of apnea and bradycardia in infants. It is also used when cardiorespiratory arrest occurs in children. It has been used in aborted SIDS episodes. It is also used to treat children who are high risk for SIDS and Cheyne Stokes respirations. However, it is of little benefit in the treatment of acute cerebral infarction, chronic bronchitis, emphysema and cystic fibrosis.

But this is a drug which is very commonly associated with adverse reactions, and is thus a frequent cause of litigation. In fact, it is included in that select small group of drugs, which cause almost 90% of all known ADRs. Yet, quite interestingly it appears in at least five "Over The Counter"

medications. It can cause such injuries as brain damage, seizures, cardiac arrhythmias, and even death.

...Written by acclaimed professionals, this comprehensive and valuable guide is a must for any professional affiliated with the pharmaceutical industry - attorneys, pharmacists, HMO and nursing home professionals, insurance claims managers, physicians and nurses. Whether you're a litigator for the defense or plaintiff, this book is packed with information to help you take the pharmaceutical case to trial. Is it the drug which caused the damage, the pharmacist's mistake in quantity, an allergic reaction, previously unknown by the patient to a certain drug, an error made by the nurse reading the quantity prescribed by the doctor, or a defect in the drug made by the pharmaceutical companies? With the myriad of possibilities, where should you start? Here is the book which will tell you exactly this... and much more!...

One of the problems with theophylline is that there is wide individual variation in the ability to clear theophylline. Half life of theophylline in asthmatics can vary as widely as between 2.4 to 20 hours. In addition, conditions such as fever decrease the ability to clear theophylline. In fact this fever issue has been central to several law suits related to theophylline, main among them being *Pollock v. Fisons* and *Klipcera v. Fisons*. This highly interesting case has been described in full detail in the book (along with several others), but an outline would be given here to give the readers a broad idea of the type of cases associated with theophylline. In this case Fisons was the manufacturer, Klipcera the physician and Pollock the affected party. Upon administration of theophylline the child developed neurological injuries, and both physician and the manufacturer were sued by the affected party. Interestingly the physician counter-sued the drug manufacturer for "failure to warn". The physician claimed that his reputation was damaged and even he claimed damages from the manufacturer. So in fact, the company found itself sued by two parties - the patient as well as his physician, while the physician was himself charged by the patient. The settlement of the case occurred like this: (i) Klipcera gave $50,000 to the affected party in an out-of-court settlement (ii) He got $ 3 million dollars from the manufacturer (iii) The company had to cough out $6.9 million for the affected party.

Readers might want to know how the physician got his money from the manufacturer and what kind of "failure to warn" was he talking about. Well, he said that the blood levels had to be taken at 24 hours, but the package insert said it had to be taken every 48 hours. Secondly the company failed to warn that the required blood level testing had to be done at all dosage levels, and not just below certain mg/kg levels as described in the package insert.

Such cases give vital insights both to drug manufacturers, as well as to physicians, as to how to avoid (or even gain from!) such litigations. For instance manufacturers might want to check their labels again before putting the drug in the market. The physician on the other hand is well-guided. He knows that such litigations can actually be productive to him! Had the affected party not sued the physician, it is quite possible that the physician might not have even thought about suing the manufacturer.

Part Three

Part three deals with pharmacy malpractice. There are chapters on regulation of pharmacy practice, nursing home pharmacy, pharmacy compounding regulations, forensic pharmacist,

forensic drug testing, Managed care in Pharmacy and the Pharmaceutical industry, medication errors, and which mistakes pharmacists most often make and why.

...[in this book] one can read about a "patient" who forged his own prescriptions for Desoxyn (a drug for weight control), and suffered addiction. He was awarded $1.8 million; about a case in which the physician and the pharmacist failed to warn the patient that the antihistaminic she was getting could cause drowsiness. As a result she fell asleep at the wheel of an automobile and was killed. Her husband got $525,000...

In the chapter on pharmacists' mistakes, several interesting case reports are given for the guidance of the reader. Read about cases where wrong dosage resulted in successful compensation suits. In one case, 100 mg Dilantin (for epilepsy) was given in place of 30 mg Dilantin resulting in a compensation of $129,000; in another 5 mg Haldol (an antipsychotic drug) was given instead of just 0.5 mg. The patient suffered dyskinesia (involuntary body movements) and was awarded $1.7 million.

Other cases are important too. One can read about a "patient" who forged his own prescriptions for Desoxyn (a drug for weight control), and suffered addiction. He was awarded $1.8 million; about a case in which the physician and the pharmacist failed to warn the patient that the antihistaminic she was getting could cause drowsiness. As a result she fell asleep at the wheel of an automobile and was killed. Her husband got $525,000. Read about a case in which a pharmacist erroneously dispensed Amantadine (AntiParkinson's and influenza preventative) in place of Cimetidine (for stomach disorders). This caused heart disorders in the patient, and he escaped death quite narrowly. The patient got $100,000 in this case. Innumerable other similar cases warn the pharmacists about the most common mistakes they make, and how they can avoid them.

There is a useful glossary at the end, giving the meaning of several terms which are not easily comprehensible in the first instance. Readers can find here definitions of such terms as Abbreviated new drug application (ANDA), Investigational new drug application (IND), Review clock and Safety update reports. Finally there are some very useful appendices.

How would I rate this book? Well, when I was reading this book, I discovered so many new facts related to drugs, especially the laws related to them, that I thought this book should be very useful for lawyers associated with cases related to drug use and injury caused by them. This book should also be very useful for all pharmacologists, pharmacists, physicians, internists, chemists, nurses, forensic physicians, drug manufacturers and in fact any one who is associated with the pharmaceutical industry or business of drugs in any way. Fully recommended reading!

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