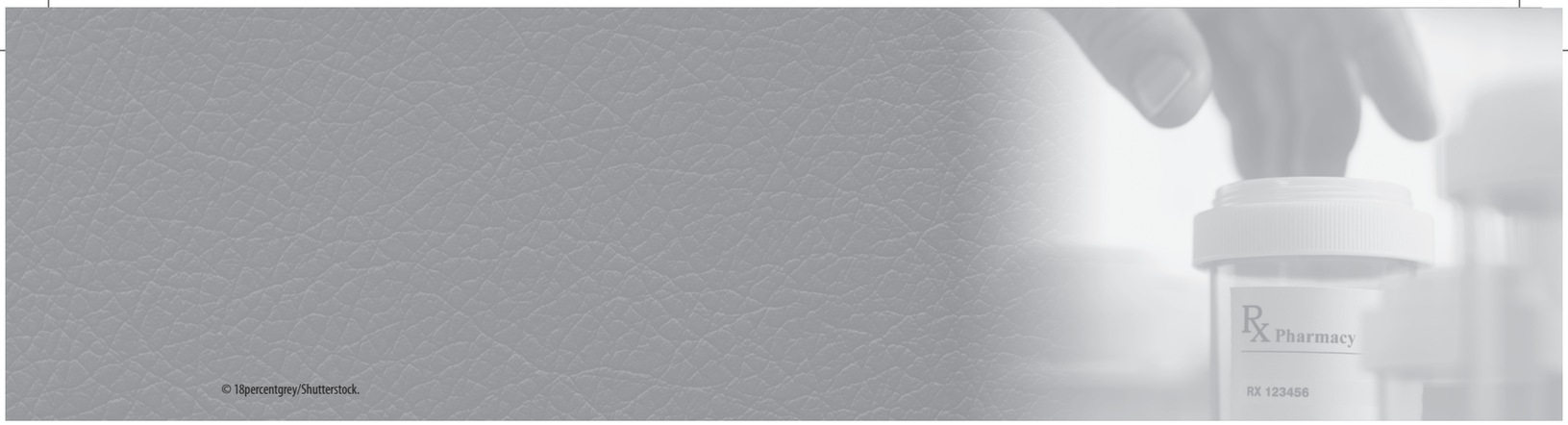


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CHAPTER 3

Federal Regulation of Medications: Dispensing

CHAPTER OBJECTIVES

Upon completing this chapter, the reader will be able to:

- Discuss the criteria by which a drug is determined to be prescription or over-the-counter (OTC).
- Understand how the provisions of the Durham-Humphrey Amendment affect drug classification and pharmacy practice.
- Describe the role of the Food and Drug Administration (FDA) in regulating written patient information, including the different types of information.
- Identify the issues associated with off-label (unlabeled) drug uses.
- Distinguish pharmacy compounding from manufacturing, including the distinctions between a § 503A compounding pharmacy and a § 503B outsourcing facility.
- Determine the role and use of the Orange Book and Purple Book in pharmacy practice.
- Identify the scope and implications of the Prescription Drug Marketing Act (PDMA).
- Recognize the requirements established in the Poison Prevention Packaging Act (PPPA).
- Understand the legal issues related to pharmacies when advertising prescription and nonprescription drugs.

The federal Food, Drug, and Cosmetic Act (FDCA) adopts a regulatory approach that emphasizes the elimination, or at least limitation, of risks throughout the drug distribution chain—from the time a scientist first imagines that a molecule might be effective as a drug through the ingestion by a patient of a product containing that drug. Pharmacists are involved with every aspect of drug development, production, marketing, and distribution. However, the primary focus of pharmacy practice is drug dispensing. In contemporary pharmacy practice, dispensing includes more than order processing. Dispensing is a comprehensive activity that incorporates drug therapy monitoring and patient education as well as drug distribution. Because most pharmacists perform dispensing functions, the aspects of the FDCA that relate specifically to dispensing are particularly relevant to pharmacy practice.

This chapter discusses regulatory activities of the FDA that have particular significance to those who are directly involved in the dispensing function and in other patient care activities.

The Durham-Humphrey Amendment of 1951

As discussed under "Misbranding," § 502 of the FDCA establishes different labeling requirements for drugs, depending on whether they are prescription or nonprescription. The questions then become: "How did it happen that we have two classes of drugs instead of one or three?" and "What determines if a drug is a prescription drug?" These answers can be found in the Durham-Humphrey Amendment, also known as the Prescription Drug Amendment (§ 503; 21 U.S.C. § 353).

Cosponsored by two pharmacist legislators, Senator Hubert Humphrey and Congressman Carl Durham, this important amendment to the FDCA created the first statutory distinction between prescription and nonprescription drugs. Legislative history of the amendment discloses that the prescription distinction from OTC was not the primary focus of the bill leading to this important law. Legalization of the verbal transmission of prescriptions (as opposed to the traditional method of writing them) and the legal right for pharmacists to honor refill authorizations indicated by physicians in the initial prescription were the key provisions of the bill. The full impact of a clear dichotomy between prescription and OTC drugs may not have been fully appreciated at the time. Although the Durham-Humphrey Amendment recognized pharmacists as being instrumental in the distribution of drugs, it failed to acknowledge that pharmacists play a significant role in drug therapy.

The Law

The amendment, as subsequently amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA), provides in part:

> (b)(1) A drug intended for use by man which—
>
> (A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or
>
> (B) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug; shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.
>
> (2) Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 502, except paragraphs (a), (i)(2) and (3), (k), and (l), and the packaging requirements of paragraphs (g), (h), and (p), if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription. This exemption shall not apply to any drug dispensed in the course of the conduct of a business of dispensing drugs pursuant to diagnosis by mail, or to a drug dispensed in violation of paragraph (1) of this subsection.
>
> (3) The Secretary may by regulation remove drugs subject to section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health.
>
> (4)(A) A drug which is subject to paragraph (1) of this subsection shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol "Rx only." (Note: prior to FDAMA the law required the label to contain the legend "Caution: Federal law prohibits dispensing without prescription." Because of this, prescription drugs have been commonly called legend drugs.)
>
> (B) A drug to which paragraph (1) of this subsection does not apply shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol described in subparagraph (A).

Explanation of the Durham-Humphrey Amendment

Before the passage of the Durham-Humphrey Amendment, drug manufacturers generally determined whether their products were prescription or OTC drugs. If the FDA disagreed with the manufacturer's choice, it had to sue the manufacturer for misbranding. There was a great deal of confusion for healthcare practitioners and patients, however, because one manufacturer could label an active ingredient a prescription drug, whereas another manufacturer labeled the same ingredient an OTC drug. The amendment resolved this situation by establishing criteria for the classification of prescription drugs. All other drugs were, of course, considered nonprescription drugs. Thus, the amendment officially established two classes of drugs: prescription and OTC.

Prescription versus Over-the-Counter Drugs

Subsection (b)(1) of the amendment provides that the FDA has the authority to categorize as prescription drugs those that are:

- Unsafe for use except under the supervision of a practitioner because of the toxicity, the method of use, or the collateral measures necessary to use the drug
- Subject to the new drug application (NDA) approval process

(*Note*: Before the FDAMA, this subsection also listed habit-forming drugs as those that the FDA could categorize as prescription.)

The issue of whether a drug requires the supervision of a practitioner for its use under subsection (b)(1)(A) and thus should be a prescription drug, was addressed in *United States v. Article of Drug—Decholin*, 264 F. Supp. 473 (E.D. Mich. 1967). In *Decholin*, the court established that the FDA must prove two issues to change the status of a drug from OTC to prescription: (1) that the toxicity and method of use require practitioner supervision and (2) that the collateral measures necessary to use the drug require supervision.

Addressing the toxicity and method of use issue, the court stated that the FDA must show that the pharmacological and toxic effect of the drug is such that, unless it is taken pursuant to a physician's directions, it may harm the patient. This requires evidence of the seriousness of harm resulting from the unsupervised use, including the dosage level that is likely to cause this harm, the immediacy of the harm, the effect of prolonging treatment by a physician, and the patient's ability to recognize that the drug is not helping before real harm occurs.

Examining the collateral measures issue, the court concluded that the government also must establish that a patient who takes the drug for a condition that the drug cannot cure will suffer harm because of the postponement of a visit to the physician in reliance on the drug. This requires the government to show the seriousness of the harm resulting from the delay, the length of delay that is detrimental, the quality of advice contained on the label (e.g., whether it alerts a patient to the possibility that professional attention may be required), and the possibility that the drug may alleviate the symptoms, making a patient think that the condition has been cured when it has not.

Dispensing Written, Oral, and Electronic Prescriptions

Subsection (b)(1) also stipulates that prescription drugs may be dispensed pursuant to written or oral prescriptions promptly reduced to writing and filed. Before the Durham-Humphrey Amendment, oral prescriptions were not valid nor were refills recognized. This subsection allows for refills, as long as they are authorized either in the original prescription or by oral order.

Note that the Durham-Humphrey Amendment does not specifically authorize the electronic transmission of prescriptions. Obviously, when Congress enacted the Durham-Humphrey Amendment it could not have contemplated electronic prescriptions (e-prescribing). Nonetheless, most states have enacted laws and regulations authorizing the transmission of prescriptions by both image transmission (fax) and data transmission. Both the FDA and DEA regard electronic prescriptions very favorably; and, the Medicare prescription drug law (Part D) specifically permits e-prescribing and preempts any contrary state restriction.

In 2000, Congress enacted the Electronic Signatures in Global and National Commerce Act known as E-Sign (P.L. 106-229). E-Sign provides that electronic records, signatures, or contracts in interstate commerce are legally valid. If a law requires a signature to be in writing, an electronic signature satisfies the law. E-Sign preempts inconsistent state laws. It is not completely clear as to the extent in which E-Sign preempts laws related to prescriptions and prescription records. If completely applicable, state and federal laws requiring pharmacies to keep paper records would be invalid if the pharmacies can maintain those records electronically. Moreover, if applicable, E-Sign would invalidate laws that require prescriptions to be handwritten or signed in writing by the prescriber.

Labeling Requirements

Without the Durham-Humphrey Amendment, pharmacists would be required to label every dispensed prescription drug pursuant to the same requirements that manufacturers must meet. Subsection (b)(2), however, recognizes that some of the information mandated by § 502 would be impractical for drugs dispensed pursuant to prescription and should fall under the discretion of the healthcare provider. Thus, subsection (b)(2) exempts the dispensing pharmacist from the labeling requirements of § 502 except for:

- The label must not be false or misleading.
- The drug dispensed must not be an imitation drug.
- The drug must not be sold under the name of another drug.
- The packaging and labeling must conform to official compendia standards.
- If it is a drug liable to deterioration, it must be packaged and labeled appropriately.
- It must be packaged in conformance with the PPPA (15 U.S.C. § 1571 et seq.).

In the case of the *Pharmaceutical Manufacturers Association v. Food and Drug Administration* (reported in the case studies section), the physician and pharmacist plaintiffs unsuccessfully argued that the exemption accorded in subsection (b)(2) precludes the government from mandating that healthcare providers distribute written information to patients for certain prescription drugs. The plaintiffs argued that because subsection (b)(2) gives them discretion regarding what information to provide to a patient, the government could not mandate that they provide written information to patients. The court disagreed, finding that it was not the intent of the provision to give complete discretion to healthcare providers to the exclusion of the government.

Subsection (b)(2) also specifies the minimum information that the pharmacist must include on the label of a dispensed drug. The law was provided earlier in this section with (b)(2) stating, in part: "the name and address of the dispenser, the serial number and date of the prescription or its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription." However, most state laws require additional information on the label:

- The name, initials, or license number of the dispensing pharmacist
- The expiration date or beyond-use date of the drug
- The drug's name, strength, and quantity dispensed
- The address of the patient
- The name of the manufacturer or distributor
- The lot or control number

It is also common that many pharmacies may include additional information on the pharmacy label above what federal and state law require. For example, a pharmacy may place the patient's address or prescriber's phone number on the pharmacy label even if it is not required under law.

State Standardized Prescription Labels

There has been increased awareness that many patients cannot read or understand the label effectively, thus leading to adverse drug events. A 2006 study, published in the *Annals of Internal Medicine*, revealed that 46% of patients misunderstood one or more instructions printed on the container labels of five commonly prescribed medications (http://annals.org/article.aspx?articleid=731144). In an effort to improve this situation, the United States Pharmacopeia (USP; http://www.usp.org) and the National Association of Boards of Pharmacy (NABP; http://www.nabp.net) have proposed that states develop standards to establish patient-centered standardized labels; and California and New York were the first two states to do so. Generally, the requirements for a patient-centered standardized label include that the label should be organized in a patient-centered manner such that critical information (i.e., name of patient, name and strength of drug, directions for use, purpose or condition) is grouped together, prominently displayed, and clear; that the critical information should be in an appropriate font size; that directions for use should be standardized and explicitly describe dosage and intervals; and when possible, the labeling should be in the patient's preferred language. California and New York require that the label be interpreted in certain languages other than English.

Other Subsection (b)(2) Considerations

Previously, subsection (b)(2) provided that if the dispensed drug was an antibiotic or insulin product subject to batch certification, then the product must have come from a batch-certified source. However, the FDAMA has since eliminated batch certification requirements.

Subsection (b)(2) does not exempt drugs from § 502 if they are dispensed pursuant to diagnosis by mail. The purpose of this provision is to help protect the consumer against fraud and quackery. It does not apply to the typical mail order drug outlets. This provision may, however, apply to situations in which

patients, who have never established a legitimate, personal physician–patient relationship, are being diagnosed and prescribed for by means of the Internet. Neither the FDA nor the courts have ever considered the application of this clause to Internet prescriptions, however.

Expiration or Beyond-Use Dating

The manufacturer is required to include the expiration date on the label of its product. This date identifies the time during which the drug may be expected to meet the requirements of the *USP* monograph for the drug. Correspondingly, many states require that the pharmacist include an expiration date or beyond-use date (BUD) of some type on the label of the dispensed drug product; however, this date may or may not be the same date as the manufacturer's expiration date, depending on state law and other factors. Once the manufacturer's container is opened and the drug product is transferred to another container for dispensing or repackaging, the manufacturer's expiration date is technically no longer valid. Thus, the *USP* states that "The dispenser shall place on the label of the prescription container a suitable *beyond-use date* (emphasis added)…" (USP General Chapter <7> *Labeling*). The "BUD" is defined as the date after which the drug should not be used, and it must not exceed the manufacturer's expiration date. The *USP* provides that in determining the BUD for all dosage forms except reconstituted drugs, the pharmacist shall take into account the nature of the drug, the container in which it was packaged by the manufacturer, the characteristics of the dispensed container, expected storage conditions, the length of the course of therapy, and other factors.

The *USP* further states that unless specified otherwise in an individual monograph or in the absence of stability data to the contrary, the BUD "shall not be later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier." For example, if you are preparing a prescription for metoprolol tablets on 11/1/18 and the manufacturer's expiration is 8/31/19, you would use the BUD 8/31/19 and not 11/1/19, since it is sooner than 1 year from the date of dispensing. It should also be noted that the manufacturer's package insert may provide information on a different BUD from the general rule just mentioned, and pharmacist's should be familiar with products that vary from the general rule. BUD standards for pharmacy compounded nonsterile and sterile drug products and for drug products repackaged by a pharmacy are different (mentioned in the compounding section of this chapter).

Pharmacists, of course, must follow state law. But, where state law is ambiguous or allows for options, many pharmacies have adopted the USP BUD guidelines, which has led to some consumer confusion. A good example of this occurred in 2003 in California. State law in California broadly requires the label to contain "The expiration date of the effectiveness of the drug dispensed" (CA B&P Code 4076(a)(9)). Rite Aid pharmacies typically affixed on the label the expiration date as being 1 year from the date of dispensing or the manufacturer's expiration date if it was sooner, pursuant to the USP guideline. At the behest of a group of consumers, the State of California brought a lawsuit against Rite Aid contending it engaged in consumer fraud for placing a misleading expiration date on the label. The suit alleged that the misleading date induced consumers to discard their medications prior to the manufacturer's expiration date and replace them, thus unfairly generating more business for Rite Aid. Once Rite Aid pointed out it was merely conforming to the USP standards, the suit was dropped.

Switch of Prescription Drugs to Over-the-Counter Drugs

As discussed earlier, subsection 503(b)(3) of the Durham-Humphrey Amendment authorizes the FDA to switch prescription drugs to OTC status by regulation when the conditions warrant. Generally, these conditions would include proof that the product can be adequately labeled such that the consumer can self-diagnose, self-treat and self-manage the condition being treated, and that the supervision of a practitioner is not required. Proof would also be required that the drug has a low potential for misuse and abuse and that the benefits of OTC availability outweigh the risks. A switch may occur in three ways:

1. The manufacturer may request the switch by submitting a NDA or supplemental application to its approved NDA (SNDA).
2. The manufacturer or other parties may request an OTC switch through a citizen petition to the FDA.
3. The FDA may add or amend an OTC monograph.

The OTC drug review process was initially the primary mechanism by which drugs were switched from prescription to OTC status. Under the review process, the advisory review panels may recommend such a switch to the FDA. If the agency agrees, it publishes a final OTC drug monograph to this effect, which becomes binding on manufacturers of that active ingredient. Today, most switches occur

through a NDA or SNDA. Using this manner, generally allows the manufacturer to obtain market exclusivity for the product.

Some switches have justifiably confused pharmacists because, on occasion, a product from one manufacturer is a prescription drug and an identical product from another manufacturer is an OTC drug. (*Note*: Differentiate this issue from how adequate directions for use labeling can cause a drug to be both OTC and prescription, as discussed under "Misbranding.") This situation can result when a switch to OTC status occurs through FDA approval of a manufacturer's NDA or SNDA. Approval for one NDA holder to switch does not automatically apply to other manufacturers of products containing the same ingredients. Each manufacturer must submit an NDA or SNDA for approval. Therefore, switches for identical products can occur at different times. Pharmacists must abide by the label and not sell a prescription drug without a prescription, even though the competitor's product may be sold OTC. A switch in status pursuant to a monograph, on the other hand, generally applies to all other manufacturers' products at the same time.

The petition route to a switch had essentially been a nonissue until Blue Cross (now WellPoint Health Networks) submitted a citizen petition to switch the nonsedating antihistamines (Allegra [fexofenadine], Claritin [loratadine], and Zyrtec [cetirizine]) from prescription to OTC in 2001. Although the regulations do not specify who may petition, no party other than a product's manufacturer had ever submitted a petition. WellPoint's petition raised the issue of whether the FDA could legally approve a petition by a party other than the manufacturer over the manufacturer's objections. Ultimately, an FDA panel voted to support the petition; but the FDA took no action, leaving it up to the manufacturers. Schering-Plough switched Claritin in 2002, Zyrtec switched in 2007, and Allegra in 2011. A complete list of drugs or drug products that have been switched from prescription to OTC since 1975 can be found at https://www.chpa.org/SwitchPP.aspx.

Third Class of Drugs

Since at least the 1970s, pharmacy organizations and others have contemplated a "third class of drugs," later called "Behind-the-Counter" (BTC) drugs and, most recently, a class of drugs that are "Nonprescription Under Conditions of Safe Use." Although the exact definition for a third class of drugs has varied, it was generally agreed that it would include certain nonprescription drugs that could be sold only by a pharmacist. The rationale for a third class of drugs is that some of the drugs being switched could jeopardize a patient's health unless a pharmacist provided appropriate consultation, and that such a class of drugs would allow the FDA to switch drugs that could not otherwise be switched because of safety concerns. Some examples of a third class of drugs do exist presently, including the sale of some Schedule V drugs in states that permit their sale as exempt narcotics.

Some question has always existed regarding whether an amendment to the Durham-Humphrey Amendment would be necessary to establish a third class of drugs on a national basis or if the FDA has the statutory authority to do so by regulation. The FDAMA included provisions for the national uniformity of nonprescription drugs, thus making it unlikely that a state would have the authority to establish a third class of drugs. Regardless, the FDA traditionally had opposed pharmacists on this issue. In 1974, FDA Commissioner A. M. Schmidt issued a policy statement that was later summarized in a 1984 petition response:

> It would be inappropriate to restrict the sale of OTC drugs to pharmacies based on anything less than proof that a significant safety issue was involved. Restricting certain OTC drugs to pharmacies only could decrease the number of outlets where the consumer could purchase OTC drug products, limit competition, and raise some OTC drug prices, with no attendant public health benefit. Recognizing at all times the important contribution of pharmacists to the healthcare system, the FDA has continued to conclude that limiting certain drugs to sale-by-pharmacists only is unnecessary because a public need for such a limitation has not been demonstrated. (Poole, 1991)

The FDA, however, first signaled a likely change in its position in 2007 by announcing a public meeting to obtain comments regarding the creation of BTC class of drugs (72 Fed. Reg. 56769, Oct. 4, 2007). The hearing was held in November 2007 where pharmacy organizations spoke in favor of a BTC category of drugs, while some other organizations, most notably the American Medical Association, opposed the category. Subsequently, the General Accounting Office issued a report on the BTC issue in 2009, comparing the U.S. regulation of nonprescription drugs to that of four European Union countries (http://www.gao.gov/new.items/d09245.pdf). The report describes pro and con arguments and identifies important policy considerations, but concludes: "The classification of drugs

in other countries and the existence of other classes provide little insight into the likely effect of a BTC drug class on nonprescription drug availability in the United States."

In February 2012, without mentioning the BTC discussions, the FDA announced that it is considering the creation of a class of nonprescription drugs that could be made available to patients "under conditions for safe use" (77 Fed. Reg. 12059, Feb. 28, 2012). The FDA noted that conditions for safe use would be specific to the drug product and could include various means, such as requiring pharmacist intervention or using innovative technologies like diagnostics, in the pharmacy or other settings. The agency held hearings in March 2012, where predictably pharmacy and insurance organizations supported the concept and medical organizations opposed it (http://www.biopharminternational.com/fda-explores-options-expand-access-nonprescription-drugs).

Professional Practice Considerations

The Durham-Humphrey Amendment directly or indirectly raises several issues of importance to professional pharmacy practice (as discussed here). State laws address many of these issues with much more specificity.

Prescription Refill Authorization

As stated in the law, a prescription may not be refilled unless there is specific authorization, either orally or in writing, from the prescriber. A physician's employee or agent, including office nurse, cannot legally authorize a refill of a prescription unless state law has specifically granted the person this authority nor can a prescriber legally delegate authority to an employee or agent not authorized by state law. The physician's employee or agent may (state law permitting), however, simply transmit or communicate the refill authorization (or new prescription) from the prescriber. In practice, this means that if a pharmacist calls a prescriber's office for refill authorization and speaks to an employee of the prescriber who immediately grants authorization, the pharmacist should question who is really authorizing the refill.

Prescriptive Authority

The Durham-Humphrey Amendment provides that prescription drugs may be prescribed by a practitioner "licensed by law to administer such drug." However, healthcare practitioners are not licensed by federal law but by state law. Thus, each state determines if a practitioner in that state has the authority to prescribe. Some states have granted various degrees of prescriptive authority not only to allopathic physicians (MDs), osteopathic physicians (DOs), dentists, podiatrists, and veterinarians, but also to nurse practitioners, physician assistants, optometrists, naturopathic doctors, and pharmacists. Pharmacists must know which categories of practitioners can prescribe in their state and be able to distinguish who falls into those categories. For example, pharmacists must understand the legal difference in their state between registered nurses and advanced practice registered nurses (APRNs). Depending on state laws, APRNs may have either independent or collaborative prescriptive authority.

In addition to ascertaining if a healthcare practitioner has prescriptive authority, a pharmacist must consider the practitioner's scope of prescriptive authority. State law (called State Practice Acts) defines a practitioner's scope of practice to diagnose and treat, which, in turn, determines the practitioner's scope of prescriptive authority. State laws grant physicians broad treatment authority and thus the authority to prescribe almost any drug. This applies even to specialists such as psychiatrists and radiologists who, because they are physicians, can legally treat conditions outside their specialty. Other prescribers such as dentists, veterinarians, and podiatrists have much narrower treatment and prescriptive authority. For example, a dentist who treats a patient for acne has very likely exceeded the scope of practice for dentistry. If the dentist then prescribed tetracycline for the treatment of the acne, the prescription would be invalid, and the pharmacist who knowingly dispensed the drug might then be in violation of the state practice act.

In reality, because a pharmacist is not usually privy to the diagnosis, determining if a practitioner is prescribing within the scope of his or her authority might be difficult to impossible in some cases. Thus, a pharmacist would not likely be held legally accountable for dispensing a prescription from a prescriber who has exceeded his or her prescriptive authority, if the pharmacist dispensed the prescription in good faith after making an attempt to ascertain the condition for which the drug was prescribed. It is important that pharmacists contact the prescriber when aware that a prescription might be outside the prescriber's scope of practice, if merely to determine if the correct drug has been prescribed.

In states that authorize nurse practitioners, physician assistants, optometrists, or pharmacists to prescribe medication, there are generally certain limits on the prescriptive authority of these professionals. The pharmacist must be aware of these limits.

Emergency Contraception (Plan B)

Before its ultimate evolution to an unrestricted OTC drug, the emergency contraception (EC) drug, Plan B, was an example of pharmacist independent prescriptive authority in some states and a third class of drugs in all states. The original Plan B, marketed by Barr Laboratories (now Teva), contains two 0.75 mg tablets of levonorgestrel to be taken 12 hours apart. EC is a method of preventing pregnancy after contraception fails or after unprotected sex and is not intended for routine use. The FDA approved Plan B as a prescription-only medication in 1999, at which point some states passed laws authorizing pharmacists to independently prescribe the drug, provided they met certain requirements. Since that time, Plan B has enjoyed a very colorful, contentious, confusing, and tortuous history.

In 2001, several medical, public health, and reproductive organizations filed a Citizen Petition with the FDA asking the agency to switch Plan B to OTC status without age restrictions. Later, in 2003, Barr submitted an SNDA to the FDA requesting a switch of the drug to OTC status without age restrictions. Despite approval for the switch by two FDA advisory committees for all age groups, the FDA rejected the SNDA application. The FDA's decision raised public outcry by many over whether politics outweighed science. The FDA, however, suggested that Barr could reapply by presenting evidence that girls under the age of 16 could use the drug OTC safely. Barr then submitted another SNDA in 2004. The FDA replied that it could not reach a decision because of three issues: (1) Whether the same active ingredient could be marketed both Rx and OTC based solely on the age of the user (rather than for different indications), (2) whether and how age-based distinctions could be enforced, and (3) whether the Rx and OTC versions may be marketed in a single package.

After considerable public controversy and FDA deliberations with Barr, the agency announced in 2006 that it had approved the amended version of Barr's SNDA application. The FDA acknowledged that Barr had submitted adequate information to demonstrate that Plan B is safe and effective for use under the labeling conditions established. Those conditions included that Plan B be sold only from BTC in pharmacies staffed by a licensed pharmacist and that the purchaser must present personal identification showing proof of age (18 or older).

The FDA set the OTC age at 18 or older, despite the fact that FDA staff agreed that Barr's SNDA established that the drug was safe and effective for 17-year-olds. Meanwhile, after a 5-year delay, the FDA denied the Citizen Petition that had been filed in 2001 seeking that the drug be available OTC for all ages. This denial prompted a lawsuit by the petitioners (*Tummino v. Torti*, 603 F. Supp. 2d 519 (E.D.N.Y 2009)). Finding for the plaintiffs, the court found that the FDA's decision had been influenced by political and ideological considerations and it had acted in bad faith and abused its discretion in denying the petition. The court ordered the FDA to make the drug available to 17-year-olds and also vacated the FDA's denial of the Citizen Petition, ordering the agency to reconsider the petition without political intrusion.

Subsequently, in February 2011, Teva Women's Health Inc. submitted an SNDA seeking to make Plan B One-Step (single dose 1.5 mg levonorgestrel approved in 2009) available OTC for all girls of reproductive age. In December 2011, the commissioner of the FDA approved the SNDA; however, the secretary of the Department of Health and Human Services (DHHS) overruled the commissioner's decision. The commissioner agreed with FDA experts that well-supported, science-based evidence existed that established Plan B is safe and effective for use in all females of child-bearing potential. Nonetheless, the secretary felt there were not enough data presented, considering the significant cognitive and behavioral differences among girls of different ages. At the same time, the FDA denied the Citizen Petition for the original Plan B (two dose) that had been remanded by the federal district court. Teva, then, submitted an amended SNDA to make Plan B One-Step available OTC to women 15 years of age and older.

The secretary's and FDA's decisions prompted the individuals and organizations that had filed the Citizen Petition to once again sue the FDA in the same federal district court (*Tummino v. Hamburg*, 936 F. Supp. 2d 162 (E.D.N.Y. 2013)) to require the FDA to make EC available without age or point of sale restrictions. On April 5, 2013, the court issued its decision, again finding for the plaintiffs. The judge commented that the secretary's directive to the FDA to reject Plan B "forced the agency to ride roughshod over the policies and practices that it has consistently applied in considering applications for switches in drug status to over-the-counter availability." The court concluded that the Secretary's decision with respect to Plan B One-Step and the FDA's decision with respect to the Citizen Petition (original Plan B) were arbitrary, capricious, and unreasonable. The court reversed the FDA's decision and remanded the Citizen Petition to the FDA, with orders to approve it and make EC products available without a prescription and without point of sale or age restrictions within 30 days.

The court ordered no point of sale restrictions after examining evidence that the current BTC restriction obstructed many women from being able to obtain the product.

On April 30, 2013, the FDA approved Teva's amended SNDA that Plan B One-Step be available for sale to those under 15 years of age "'proof of age required' not for sale where age cannot be verified." The product would be available only in retail outlets with an onsite pharmacy, but inventoried in an aisle and available during the retailer's normal operating hours whether the pharmacy is open or not. The announcement noted that the FDA's decision was independent of the litigation and not intended to address the court's decision. Then, one day later, the Department of Justice announced it would appeal the district court's decision and seek to delay the decision.

On appeal, a three-judge panel of the Second Circuit Court of Appeals on June 5, 2013, refused to delay the district court's order for two-dose (0.75 mg) EC products, thus requiring the FDA to make them available immediately without age restriction (*Tummino v. Hamburg*, 2013 WL 2435370 (2d Cir. 2013)). The panel did stay the district court's order for Plan B One-Step pending an expedited appeal. Ultimately, however, the FDA decided not to appeal, and on June 20, 2013, it issued an announcement that it was complying with the district court decision and had approved an amended SNDA from Teva for Plan B One-Step without age or point of sale restriction. Teva received 3 years of exclusivity on Plan B One-Step.

Currently, there are a variety of brands of levonorgestrel morning-after pills OTC available without a prescription at pharmacies. However, it should be noted that not all EC is OTC, for example, the medication ella that currently requires a prescription to obtain.

Conscientious Objection

Prescriptions for EC drugs, abortifacient drugs, and oral contraceptives have raised a very contentious issue: whether a pharmacist has a right to refuse to dispense prescriptions to which the pharmacist has moral or religious opposition. This issue has been labeled as one of conscientious objection and has been the subject of discussion among the media, Congress, state legislators, and professional organizations. It has resulted in legislation and/or board of pharmacy regulations in many states as well as professional organization guidelines; however, no consensus has really emerged. Some states have passed laws or regulations requiring pharmacists to dispense prescriptions regardless of their moral beliefs. Some states have enacted laws establishing "conscience clauses," such that pharmacists may refuse to dispense prescriptions that violate their conscience.

Professional organizations and state boards of pharmacy generally have taken a compromise position, attempting to respect the pharmacist's beliefs while ensuring that patients receive the medications to which they have a legal right. Under this philosophy, a pharmacist should notify the employer in advance and in writing of his or her objections to dispense particular drugs. The employer, provided it can do so without undue hardship, should develop procedures such that the pharmacist is not placed in a situation where he or she would be required to dispense the objectionable prescriptions, and yet that still allow the patient to receive the drug with minimal inconvenience. For example, another pharmacist on duty could dispense the medication or the patient could be referred to a nearby pharmacy.

In no situation should a pharmacist obstruct a patient's legal right to receive a lawful medication. In the case of *Noesen v. State, Dept. of Regulation and Licensing*, 754 N.W.2d 849 (Wis. 2008), a Wisconsin pharmacist informed the employer of his conscientious objection to dispense birth control prescriptions, but did not tell the employer that he would not transfer refills upon the request of another pharmacy. When a patient attempted to refill her birth control prescription, the pharmacist told her he could not dispense it and that there was no other pharmacist on duty. The patient then went to another pharmacy but the pharmacist refused to transfer the prescription to the pharmacy, resulting in the patient missing a dose. The State Board of Pharmacy found the pharmacist guilty of unprofessional conduct, because his failure to transfer the prescription constituted a danger to the health and safety of the patient and substantially departed from the standard of care of a pharmacist. The Board ordered that the pharmacist inform all future employers in writing that he would not dispense birth control prescriptions and outline the steps he would take to ensure that a patient has access to the medication. The pharmacist sued the Board, but the Wisconsin court of appeals upheld the Board's decision.

However, in a situation in Idaho, a prescriber phoned in a prescription to a pharmacist for Methergine, a drug generally used for the prevention and control of postpartum hemorrhage. The pharmacist asked if the drug was for postabortion care and the prescriber replied that she could not disclose that

information because of confidentiality. The pharmacist said she would not dispense the prescription and hung up when the prescriber requested a referral to another pharmacy. A complaint was filed with the board of pharmacy that found no violation of Idaho pharmacy laws or regulations under Idaho's conscience clause law (NABP Newsletter, 2011).

In a State of Washington case, the issue centered upon whether board of pharmacy regulations requiring pharmacies to dispense lawfully prescribed drugs except under certain circumstances violated the plaintiff pharmacists' constitutional rights (*Stormans, Inc. v. Selecky*, 844 F. Supp. 2d 1172 (W.D. Wash. Feb. 22, 2012)). After 4 years of litigation, a federal district court determined that the Washington regulation violated the plaintiff pharmacy's and pharmacists' First Amendment rights to the free exercise of religion as well as their rights to equal protection under the Fourteenth Amendment. The Ninth Circuit Court of Appeals, however, reversed the decision (*Stormans, Inc. v. Wiesman*, 794 F.3d 1064 (2015)), and the U.S. Supreme Court refused to hear the case (136 S.Ct. 2433 (June 28, 2016)). Thus, the Washington regulation remains in effect.

At the federal level, the U.S. DHHS established a new division within its Office for Civil Rights (OCR) in 2018 known as the Conscience and Religious Freedom Division. The purpose of this division is to enforce existing federal laws that protect healthcare workers from performing, assisting with, training for, or making referrals for healthcare procedures that are morally objectionable to the healthcare professional. At the same time, DHHS published a proposed rule confirming and expanding its enforcement authority to protect health professionals asserting conscience and religious freedom objections (83 Fed. Reg. 3880 (January 26, 2018)). It is not clear at this time what affect these federal developments will have on state laws and judicial decisions related to conscientious objection in pharmacy practice.

Collaborative Practice Agreements

Although pharmacists do have limited prescriptive authority in some states for certain drugs, they do not have unrestricted independent prescriptive authority in any state. However, most states have enacted legislation allowing pharmacists to initiate or adjust drug therapies in collaboration with a physician. This collaborative arrangement requires a written contractual agreement in the form of protocols and procedures. The extent to which a pharmacist may engage in drug therapy management often depends upon state law, the collaborative agreement, and the practice setting. Authority granted to the pharmacist can range from following a restrictive drug formulary to having complete discretion to select any drug the pharmacist deems best.

Authority to Dispense Prescription Drugs

The FDCA does not specify who may or may not dispense prescription drugs; this again is the jurisdiction of the states. Pharmacists licensed to practice under state law may dispense prescription drugs, of course, as may any other practitioner who is authorized to do so under a state's laws, including physicians.

Physician dispensing increased significantly in the 1980s as physicians sought ways to supplement their incomes, lowered as the result of both managed care and governmental cost containment efforts. Pharmacists strongly oppose physician dispensing on economic and ethical grounds and were particularly irked that physicians in many states did not conform to the same dispensing standards required of pharmacists. Some physicians, for example, poured tablets and capsules in sacks and either wrote the directions on the sack or merely told the patient the directions. Looking for ways to curb the practice of physician dispensing or at least to hold physicians to dispensing standards, pharmacists asked the FDA to step in and apply the Durham-Humphrey Amendment's standards to physicians. On the basis of its interpretation of congressional intent, however, the FDA took the position that the labeling requirements of the law apply only to pharmacists, not physicians.

The wisdom of the FDA's interpretation aside, many states enacted legislation in the 1980s mandating that dispensing physicians meet the same or similar dispensing requirements as pharmacists. One state pharmacy board went a step further, and proposed regulations placing greater dispensing restrictions on physicians than pharmacists. This prompted the Federal Trade Commission (FTC) to threaten legal action against the pharmacy board. The FTC viewed the proposed regulations as anticompetitive in violation of the antitrust laws, because one group of competing professionals was unduly restricting another group for economic advantage. The board subsequently amended its regulations to impose the same restrictions on physicians as pharmacists.

Federal law does place some restrictions on physician dispensing through the Medicare/Medicaid fraud and abuse statutes. Federal law also prohibits physicians from referring Medicare and Medicaid patients to pharmacies that they own.

TAKE-AWAY POINTS

- The Durham-Humphrey Amendment established the criteria for differentiating between prescription and OTC drugs; the legality of orally communicated prescriptions; the legality of refills; and labeling requirement exemptions for drugs dispensed pursuant to prescriptions.
- Some states now require patient-centered standardized labels on the containers of dispensed drugs.
- When determining an expiration or BUD for the label of a dispensed drug in a multiple unit container, pharmacists must interpret state law and, if allowed, can follow USP guidelines.
- When determining an expiration or BUD for the label on a drug repackaged into a unit-dose container, pharmacists must interpret state law together with USP and FDA guidelines.
- The FDA can authorize a switch of a drug from prescription to OTC status by means of an approved NDA or SNDA, a petition, or by adding or amending an OTC monograph.
- Historically opposed to the concept, the FDA may now be favorable to the creation of some type of a "third class of drugs" by first exploring a BTC class of drugs and, most recently, discussing a class of drugs that could be made available to patients "under conditions for safe use."
- Only a prescriber can authorize a refill; however, authorized agents of the prescriber can transmit the prescriber's refill authorization.
- State law determines prescriptive authority and pharmacists must be aware of not only who is authorized to prescribe, but also the scope of that prescriptive authority.
- The EC, Plan B, has experienced a tortuous regulatory history, ultimately ending up as an OTC drug without age and point of purchase restrictions.
- Pharmacists who have a conscientious objection to dispensing particular medications should be aware both of their rights as determined by state laws and the patient's legal and ethical rights.
- State law determines who can dispense prescriptions, including physicians, although state laws or regulations cannot restrict physicians more than pharmacists or pharmacies without valid justification.

STUDY SCENARIOS AND QUESTIONS

1. The FDA has decided to switch an OTC drug to prescription only. The manufacturer has sued the FDA to prevent the switch. What must the FDA prove in court in order to prevail in this lawsuit?
2. The expiration date on the labeling of the manufacturer's prescription drug container is 12/20. The pharmacist dispenses the prescription on 3/21/19 in the same container; however, the pharmacy labels the expiration date as 3/21/20. The patient asks the pharmacist why the dates differ. What explanation should the pharmacist provide? Is the date the pharmacist included on the label proper? What if the drug was dispensed in unit dose containers?
3. A manufacturer would like to have its drug product switched from prescription to OTC. What procedures can a manufacturer follow in order to attempt this? What might the manufacturer likely have to prove to affect the switch?
4. A pharmacist received a prescription from a psychiatrist for a cardiac antiarrhythmic drug. Explain if it would violate the law to dispense this prescription and the procedure that the pharmacist should follow in this situation.
5. A pharmacist received a prescription from a dentist for an antibiotic written to take tid for a urinary infection. Explain if it would violate the law to dispense this prescription and the procedure that the pharmacist should follow in this situation. How does this situation differ from the previous one?
6. A patient presents a pharmacist with a prescription for a drug product that can be used to induce abortion. The pharmacist is opposed to abortion and refuses to fill the prescription. What is the pharmacist's legal responsibility in your state? How might this situation have been avoided?

Prescription Drug Labeling Information for the Patient

As you learned in other sections of this book and the discussion of the Durham-Humphrey Amendment, prescription drug labeling by manufacturers is directed at the healthcare professional, not the patient. There are, however, two types of labeling mandated by federal law that manufacturers must supply for the patient package inserts (PPIs) and medication guides.

Patient Package Inserts

Until the late 1960s, the FDA had not devoted much attention to the issue of manufacturers providing prescription drug labeling directed to the patient. The FDA's inattention to this issue changed dramatically

in 1970 when it issued a regulation requiring that information for the patient called PPIs accompany oral contraceptive drugs explaining the drugs' uses, risks, and precautions (21 C.F.R. § 310.501). The agency initiated this action because of the widespread popularity of oral contraceptives and the relative lack of awareness by women of the drugs' potential serious adverse effects, especially thrombophlebitis and pulmonary embolism. If this information is not contained on or in the product package, it must be provided as leaflets with the product. Furthermore, the manufacturer must instruct the pharmacist to distribute a leaflet with each prescription.

On the heels of this regulation, the FDA enacted regulations in 1977 requiring PPIs for estrogen-containing drugs (21 C.F.R. § 310.515), such as conjugated estrogens and diethylstilbestrol (DES) not intended for oral contraceptive use, and progestational drugs (21 C.F.R. § 310.516). The PPI requirement for progestational drugs was repealed in 1999; however, if a progestational drug is intended for use as an oral contraceptive, then the oral contraceptive PPI is required. (*Note*: The FDA issued a draft guidance for noncontraceptive estrogen drug products in November 2005 (https://www.gpo.gov/fdsys/granule/FR-2005-11-16/05-22754/content-detail.html). The authority of the FDA to promulgate these regulations was upheld in the case of *Pharmaceutical Manufacturers Association v. Food and Drug Administration* (discussed in detail in the case studies section of this chapter).

Manufacturers must include a PPI for each package that it intends will be distributed to the patient, and in turn, pharmacists must include a PPI with each container dispensed regardless of whether it is initially dispensed or a refill. Failure to do so is misbranding. PPI regulations apply not only to community pharmacies, but also in a modified form to institutions. An institution may provide the PPI to the inpatient the same as to an ambulatory patient, or it may provide the PPI before the administration of the first dose and then once every 30 days thereafter. In *Schlieter v. Carlos*, Nos. 87-0955 SC, 11592 SC (D.N.M. Aug. 1989), an inpatient contended that the hospital was negligent in not providing her with a PPI when she was given estrogen (Premarin). The defendant hospital argued that it had a right to rely on the treating physician to provide the PPI if the physician so wished. The court disagreed, establishing that an institution cannot delegate its responsibility for providing a PPI to the prescribing physician. The court concluded that the intent of the regulation is that patients, not physicians, must be given the information.

Firmly believing in the importance of written drug information for patients, the FDA in 1980 enacted regulations requiring PPIs for all prescription drugs (45 Fed. Reg. 60754, Sept. 12, 1980). The proposal received strong opposition, however, from physician and pharmacy organizations on the grounds that the program would be unduly expensive and burdensome for providers and would not achieve the patient outcomes desired. Many of these organizations then proposed alternative means of providing information to the patient, causing the FDA to agree that private sector initiatives were preferable to a government-mandated program and to revoke the regulations (47 Fed. Reg. 39147, Sept. 7, 1982).

Useful Written Patient Information and Medication Guides

Not satisfied, however, with private sector efforts to provide prescription drug information to patients, the FDA in 1995 published a proposed rule that would have implemented a new patient information program (60 Fed. Reg. 44182, Aug. 24, 1995). The program consisted of two parts. One part would require that manufacturers provide Medication Guides (MedGuides) for a few specifically designated drugs that pose a "serious and significant" concern to public health. The second part mandated that "useful" written patient information (now called consumer medication information (CMI)) be given to the patient for every drug each time a new prescription is dispensed.

The goal of the program was to ensure that all patients receive comprehensive written information about their prescribed drugs to supplement oral counseling from healthcare professionals. The FDA believes that this patient information is necessary for patients to use drug products safely and effectively. In turn, commented the agency, substantial healthcare cost savings would result by "reducing the harm caused by inappropriate drug use and enhancing the benefits of drugs by facilitating their proper use."

Consumer Medication Information

Regarding the second part of the program—that useful written patient information (CMI) accompany every new prescription—the agency proposed distribution goals and performance standards for patient information and left it up to the private sector to accomplish them. If the private sector failed to reach these goals and meet the standards, the agency indicated that it would then become necessary to federally establish a comprehensive patient information program.

The program proposal generated considerable controversy, especially among pharmacy organizations and

pharmaceutical manufacturers who resented the FDA's intrusion. Shortly thereafter, Congress enacted legislation that established a voluntary private sector process under which national organizations of healthcare providers, consumers, pharmaceutical companies, and others could collaborate to achieve the program's goals but without the threat of a federally mandated program (P.L. 104-180, Sept. 30, 1996). The law required that 95% of patients receiving new prescriptions receive useful written information about their medications by 2006. Failure of the private sector to implement a program within 4 years of the law's passage would result in reinstatement of the original FDA-mandated proposal. Pursuant to this requirement, private sector stakeholders met to assess the effectiveness of current oral and written patient information, developed guidelines based upon this assessment, and developed a process to continually evaluate the quality and frequency of the information provided to patients. This collaboration program was completed and its plan accepted by the FDA prior to the deadline.

Assessing the progress of the private sector plan, an FDA-commissioned study in 2001 found that although 89% of patients with new prescriptions received written information, the information was useful to patients only about 50% of the time (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm169753.htm). In order to assist the private sector in meeting the 95% goal, the FDA published a guidance titled "Guidance: Useful Written Consumer Medication Information (CMI)" in July 2006 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory-Information/Guidances/UCM080602.pdf). The guidance provided recommendations on what information should be provided and how it should be provided. The FDA noted that failure of pharmacies and others to meet these CMI standards voluntarily could result in the FDA resorting to mandatory measures. In December 2008, the FDA released the results of a follow-up study (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunication-AdvisoryCommittee/UCM117149.pdf) showing that although more consumers were receiving CMI (94%), only about 71% of this information met the minimum standard criteria for usefulness. (Recall the law required 95%.) An FDA official remarked: "The current voluntary system has failed to provide consumers with the quality information they need in order to use medicines effectively and safely" (Janet Woodcock, MD, director of the Center for Drug Evaluation and Research, *FDA News*, December 16, 2008). Flaws found in CMI include formatting that is too small and crowded, inconsistent word counts with some CMI being extremely lengthy and repetitive, lack of clear action steps patients should take in the result of an adverse event, lack of clear organization and prioritization of information, and cluttering of important information with unnecessary verbiage. Nonetheless, CMI remains unreviewed and unregulated by the FDA.

Medication Guides

After passage of the 1996 law, the FDA acknowledged that the law had stripped it of its authority to establish a comprehensive private sector patient information program for all drugs. However, it felt that it retained the authority to mandate the Medication Guide program for drugs posing a "serious and significant concern," and therefore enacted a final regulation to this effect in 1998 (63 Fed. Reg. 66378; 21 C.F.R. parts 201, 208, 314, 601, and 610). The regulation specified that Medication Guide requirements primarily apply to outpatients who are not under the direct supervision of a healthcare professional and apply to both new and refill prescriptions. Under the final regulation, patient labeling for a product is required if the FDA determines that one or more of the following circumstances exists regarding a drug product: (1) that patient labeling could help prevent serious adverse effects; (2) that the product has serious risks relative to its benefits of which the patient should be aware in order to decide whether to use or continue to use the product; and (3) that patient adherence to directions is crucial to the drug's effectiveness. The FDA acknowledged that the MedGuides would be required for very few products, "no more than 5 to 10 products per year."

In November 2011, the FDA published a guidance document explaining when the agency will require that a MedGuide be provided to a patient and when a MedGuide will be required as part of risk evaluation and mitigation strategy (REMS) (http://www.fda.gov/downloads/Drugs/Guidance-ComplianceRegulatoryInformation/Guidances/UCM244570.pdf). The guidance articulates that, in general, a MedGuide need not be provided when the drug is dispensed to a healthcare professional for administration to a patient in an inpatient setting or in an outpatient setting such as in a clinic or dialysis or infusion center. However, the guidance then lists exceptions and other situations where the MedGuide is mandatory, including:

- When the patient or patient's agent requests a MedGuide
- When the drug is dispensed in an outpatient setting and the patient will use the drug without direct supervision of a healthcare professional (e.g., community or hospital ambulatory care pharmacy)

- The first time a drug is dispensed to a healthcare professional for administration to a patient in an outpatient setting such as in a clinic or infusion center
- The first time a drug is dispensed in an outpatient setting of any kind after a MedGuide is materially changed
- When a drug is subject to a REMS that includes specific requirements for reviewing or providing a MedGuide

Pursuant to the regulation, MedGuides must be written in nontechnical language and in a uniform format, containing the approved uses for the product, circumstances when the product should not be used, serious adverse reactions, proper use, cautions, and other general information. The manufacturer of the drug product for which a MedGuide is required must obtain FDA approval before the guide is distributed with the product. Manufacturers must provide directly or supply the means to provide sufficient numbers of the MedGuides to the distributor or dispenser of the product. The dispenser, in turn, must provide the guide to the patient each time the medication is dispensed when required. It is important to note that other written drug information the pharmacy may distribute does not replace the MedGuide. A study conducted by the FDA in 2004 of 5,000 pharmacists determined that 29% of pharmacists were not familiar with medication guides (from transcripts: http://www.fda.gov/Drugs/DrugSafety/ucm172845.htm).

The FDA has significantly increased the number of drugs subject to MedGuides over the past few years, now requiring nearly 800 drug products to have MedGuides. A list of those drugs can be accessed at http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm. The number of MedGuides has raised concerns from pharmacy organizations over the administrative burdens and distribution difficulties MedGuides cause pharmacies and their impact on pharmacy workflow. Because of the concern over MedGuides and the fact that Congressional goals had not been met for CMI, the FDA convened the Risk Communication Advisory Committee in February 2009 and encouraged public participation. The Agency also held a public workshop in September 2010 seeking answers as to the best ways to provide useful prescription information to consumers. The Agency announced a goal that envisioned a single, easy-to-read document incorporating the most important information from PPIs, CMI, and MedGuides that the FDA now collectively terms "patient medication information" or PMI (https://www.federalregister.gov/documents/2010/08/27/2010-21326/development-and-distribution-of-patient-medication-information-for-prescription-drugs-public-hearing). Although this vision has yet to materialize, the FDA in February 2017 discussed the issuance of a proposed rule that would require manufacturers to produce a one page document highlighting for patients the most important information about the drug (http://www.raps.org/Regulatory-Focus/News/2017/02/23/26945/FDA-Discusses-Upcoming-Proposed-Rule-on-One-Page-Patient-Medication-Information). This one page document would not replace any currently required professional labeling.

Medication Guides and REMS

The Food and Drug Administration Amendments Act (FDAAA) of 2007 authorized the FDA to require REMS when necessary to ensure that a drug's benefits outweigh its risks and MedGuides are an important component. The FDA can require a REMS both prior to NDA approval and postmarket. The compliance guide stipulates that since the FDAAA was enacted in 2007, the FDA has considered every new MedGuide to be part of a REMS. However, as the agency states in the 2011 compliance guidance, it has the discretion to determine that a new MedGuide should be required as labeling only, not part of a REMS.

Drug Information Website for Pharmacists: Drug Info Rounds

At the FDA website, pharmacists can access "Drug Info Rounds"—a series of training videos providing important and timely drug information to pharmacists in order to assist them in helping patients make better medication decisions (http://www.fda.gov/drugs/resourcesforyou/healthprofessionals/ucm211957.htm).

Drug Information Website for Consumers and Health Professionals: Drugs@FDA

In addition to the patient-directed labeling required of manufacturers, the FDA provides its own source of drug information for consumers and healthcare professionals. Accessible through the FDA's home page or directly at https://www.accessdata.fda.gov/scripts/cder/daf, the website called Drugs@FDA provides a searchable database that includes information on approved prescription drugs, some OTC drugs, and even discontinued drugs. Individuals can search by drug name or active ingredient and obtain essentially all relevant labeling information about the drug, including therapeutically equivalent drugs and the approval history.

TAKE-AWAY POINTS

- Community pharmacies and, in many situations, institutional pharmacies must dispense PPIs to patients for oral contraceptives, estrogen-containing drugs, and DES drugs.
- CMI is written information other than a PPI or MedGuide that a pharmacy distributes to a patient and is not reviewed by or regulated by the FDA.
- The FDA requires that manufacturers produce and that pharmacies dispense MedGuides for drugs that pose a "serious and significant concern."
- Subject to certain exceptions, a MedGuide is not required when the drug is dispensed to a healthcare professional for administration to a patient in an inpatient setting or in an outpatient setting such as in a clinic or dialysis or infusion center.
- The FDA may require that a MedGuide be all of or part of a REMS, or simply be required as labeling.
- The FDA maintains websites where healthcare professionals and patients can access medication-related information.

STUDY SCENARIOS AND QUESTIONS

1. A community pharmacy dispenses prescriptions to a patient for conjugated estrogen, warfarin, and amoxicillin. Discuss what type of written patient information is required for each of these drugs, if any.
2. A hospital pharmacy dispensed DrugX to an inpatient pursuant to a medication order. A MedGuide is available for DrugX. When the nurse administered the drug to the patient, the patient asked if there is any literature that she could read about the drug. The nurse replied that the hospital did not have any and the patient then asked to speak to a pharmacist. If you were the pharmacist, what should you do and what does the FDA guidance recommend?

Approved Drugs for Off-Label (Unlabeled) Indications

The promotion of drug products by manufacturers for "off-label" uses is controversial, subject to significant restrictions and could constitute misbranding. Nonetheless, healthcare professionals commonly prescribe and dispense many drugs for indications other than those listed in the approved labeling. These off-label uses may even constitute the medically accepted standard of care for treatment. This is especially true in the treatment of cancer and human immunodeficiency virus infection. There are many reasons why some indications for a drug's use are not included in the approved labeling. One reason is that practitioners find promising uses for drugs much faster than the drug regulatory system can approve those uses. Another reason is that manufacturers commonly seek NDA approvals for a minimal number of indications so that they can expedite the approval process and market their drugs as soon as possible, generally with the intent to submit an abbreviated new drug application (ANDA) or SNDA to have the additional indications added to the labeling at a later date.

When a drug is prescribed for a condition not listed in its official labeling, this use is called off-label, unlabeled, or unapproved. The FDA has taken the position that a drug may be legally prescribed and dispensed for an off-label indication or dosage. In a 1972 proposal statement, the FDA announced:

> If an approved new drug is shipped in interstate commerce with the approved package insert and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of § 505 of the Act are satisfied. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration (37 Fed. Reg. 16503, Aug. 15, 1972).

In testimony to a Congressional committee in 1996, an FDA spokesperson stated: "… in certain circumstances, off label uses of approved products are appropriate, rational, and accepted medical practice" (Schultz, W.B). More recently, the FDA indicated the same position in a compliance guidance on off-label uses (https://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm). The Omnibus Budget Reconciliation Act of 1990 (OBRA '90) also seems to

recognize the medical importance of off-label indications by accepting information in professional compendia (which often list a drug's off-label indications in addition to its labeled indications) as a standard in determining appropriate drug use for Medicaid patients. However, some contend that OBRA '90 actually restricts off-label indications because many off-label indications are not stated in compendia sources.

Clearly, the act of prescribing and dispensing approved drugs for off-label indications is less an issue of labeling or misbranding than it is an issue of eliminating unreasonable risks. From a practical perspective, pharmacists must exercise professional judgment. If a drug is prescribed for either a labeled or an off-label indication and there is no unreasonable risk to the patient, the pharmacist may dispense the drug. If the risk to the patient is unreasonable, the pharmacist has a duty to take additional action. The pharmacist should contact the prescriber to confirm that the proper drug or dosage has been prescribed. In situations in which the patient is at significant risk of harm, the prescriber should justify the decision to the pharmacist. These actions are important, both to protect the patient and to reduce the risk of civil liability because the use of a drug for unlabeled indications may create a greater risk of civil liability in the event of patient injury. In *Mulder v. Parke-Davis & Co.*, 181 N.W.2d 882 (Minn. 1970), the court considered the package insert as prima facie evidence of negligence, shifting to the physician the burden of establishing why he or she deviated from the labeling. However, more recent decisions such as *Ramon v. Farr*, 770 P.2d 131 (Utah 1989), reported in the case studies section of the chapter, hold that the package insert is only evidence of the standard of care, placing the burden of proof on the plaintiff to establish the practitioner did not meet the standard of care.

As another practical matter, pharmacists must be aware that certain third-party insurance and managed healthcare plans will not compensate providers for drugs prescribed and dispensed for off-label indications.

Pharmacists who provide drug information to other healthcare providers regarding off-label indications generally need not fear violating the FDCA as long as the intent of the information is advisory or educational, not promotional. In *United States v. Evers*, 643 F.2d 1043 (5th Cir. 1981), the court held that a physician who publicly advocated calcium disodium edetate for unapproved use as a chelating agent did not violate the FDCA. The physician was not selling the drug to other physicians or pharmacies, but merely distributing the drug to his own patients within his own practice of medicine.

TAKE-AWAY POINTS

- Although the promotion of drug products for off-label uses is subject to restrictions and could constitute misbranding, healthcare professionals may legally prescribe and dispense drugs for off-label uses.
- The FDA takes the position that off-label use in general is acceptable medical practice.
- Pharmacists dispensing drugs for off-label use should exercise professional judgment and evaluate the risks to the patient.
- Generally, in a negligence lawsuit, the labeled indications are only considered as evidence of the standard of care.

STUDY SCENARIOS AND QUESTIONS

1. Dr. Bill is a hospital pharmacist making rounds with a physician, Dr. Jake. One of Dr. Jake's patients had just been admitted to the hospital in premature labor. Unable to reduce the contractions, Dr. Jake consulted with Dr. Bill about administering terbutaline sulfate. The drug has FDA approval only for use in bronchial asthma, but was also being widely used as a tocolytic agent because it relaxes smooth muscles. Dr. Bill had reservations because the labeling for terbutaline states

   > …is indicated for the prevention and reversal of bronchospasm in patients with bronchial asthma and reversible bronchospasm associated with bronchitis and emphysema. ***Terbutaline sulfate should not be used for tocolysis. Serious adverse reactions may occur after administration of terbutaline sulfate to women in labor. In the mother, these include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia.

Nonetheless, Dr. Bill agreed with Dr. Jake that this was the best course of therapy. After 48 hours of dosing, the contractions stopped. Shortly thereafter, the patient suffered a heart attack, delivered a healthy baby, and underwent open-heart surgery. The patient subsequently sued both Dr. Bill and Dr. Jake.

a. Did Dr. Bill or Dr. Jake violate the FDCA?
b. If you were Dr. Bill, what would you have done?
c. Should the patient have been told of the risks?
d. Should the patient have been told the drug was being used off-label?
e. When would you not dispense or prescribe a drug for an off-label use?
f. How much evidentiary weight should the labeling be given in the malpractice lawsuit?

2. A patient who has recently been dispensed a prescription medication angrily confronts the pharmacist. The patient has read the CMI included with the product and notes that the drug is not indicated for the purpose for which the drug was prescribed. The patient wants to know if the drug is correct and, if so, why it was prescribed and dispensed. What should the pharmacist do?

Pharmacy Compounding Versus Manufacturing

Long before the existence of pharmaceutical manufacturers, pharmacists compounded medications for their patients. Eventually, however, manufacturers began producing an ever-increasing number of products in finished form, obviating the need for pharmacy compounding in most situations. Nonetheless, compounding has enjoyed a resurgence of popularity as pharmacists prepare significant numbers of intravenous products, radiopharmaceuticals, chemotherapeutic agents, topical preparations, suppositories, veterinary medications, and even tablets and capsules.

Section 510(g) of the FDCA provides in part that pharmacies are exempt from registering as manufacturers if they:

> … do not manufacture, prepare, propagate, compound or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail (§ 510(g); 21 U.S.C. § 360(g)).

Section 510(g) recognizes that the traditional compounding by pharmacists, which is regulated by state law, is not manufacturing. The pharmacy exception provided by this section is important because a pharmacy that is deemed a manufacturer must obtain a license from the FDA, most likely obtain an approved Investigational New Drug (IND) application, and conform to the regulations regarding current good manufacturing practice (CGMP). Pharmacies that repackage OTC products or in any way change the container, wrapper, or labeling of these products for resale must also register as manufacturers (§ 510(a)(1)). Thus, pharmacies in the business of repackaging prescription drug products for sale to other healthcare providers must register as manufacturers. Pharmacists who dispense to long-term care facilities (LTCFs) have expressed concern regarding whether they violate federal and state laws when they repackage and relabel drugs dispensed by another pharmacy. This situation may occur when a patient is admitted to the LTCF and brings along medications the patient has been taking at home. The LTCF might then send the patient's medications to the contracting pharmacy for repackaging into packaging compliant with the LTCF's policies. Although the FDA has never issued an opinion on this practice under federal law, some states have enacted laws or regulations to authorize the practice.

Historically, there has been considerable friction between the FDA and the pharmacy profession over the interpretation of the compounding exemption. The FDA first became quite concerned about pharmacy compounding in light of problems that resulted in patient injuries. In 1989, for example, a Pittsburgh pharmacist prepared indomethacin eye drops that resulted in eye infections in 12 patients. Two of these patients had to have an eye surgically removed. The same year, patients died because a hospital pharmacy in Lincoln, Nebraska, prepared surgical solutions that became microbially infected. As a result, the FDA published an Alert Letter on compounding in November 1990, expressing concern that some pharmacies were using incorrect procedures and controls when compounding sterile products (Bloom, 1991). The FDA emphasized that pharmacists who prepare batches of sterile drug products are responsible for conforming to CGMP and for using safe packaging to ensure continued sterility during use. The letter also warned pharmacists to balance their need to prepare batches of sterile products with their capacity for doing so. The FDA concluded that it did not wish to discourage

pharmacists from compounding, but offered the letter as a "strong reminder" to pharmacists of the seriousness of batch-producing sterile drugs.

A substantial amount of legislative, regulatory, and judicial activity over compounding has occurred since 1990. This activity will be addressed here in some detail, because understanding the historical evolution of compounding is important to understanding the regulatory framework as it exists today.

FDA 1992 Compliance Policy Guide

After the Alert Letter, state and national pharmacy organizations became concerned that the FDA was intent on eliminating the right of pharmacists to compound medications as part of their ordinary practice. This concern led to several meetings between pharmacy organizations and the FDA, resulting in the publication of a compliance policy guide (CPG) in March 1992. The CPG emphasized that the FDA had no intention of regulating pharmacy's historic exemption to compound drugs extemporaneously in reasonable quantities pursuant to prescription. The guide also stated that pharmacists may also prepare "very limited quantities" of drugs before receiving valid prescriptions, provided that these anticipated quantities can be documented historically with prescriptions on file. However, the FDA stated:

> FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing, distributing, and promoting unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that constitute violations of the Act (Compliance Policy Guide 7132.16 at 2).

This statement primarily reflected the FDA's concern with pharmacies that compounded drugs on a large scale and sold them in large quantities to other entities such as hospitals, clinics, and physicians' offices—in essence, acting as manufacturers. However, many compounding pharmacists believed that the statement reflected the agency's negative feelings about pharmacist compounding and that the FDA's enforcement activities were too intrusive. This controversy prompted Congress to clarify the distinctions between compounding and manufacturing in the FDAMA of 1997.

FDAMA's Compounding Provisions (§ 503A)

FDAMA amended the FDCA (§ 503A; 21 U.S.C. § 353a), effectively rescinding the 1992 CPG. The FDAMA compounding law (§ 503A) helped clarify for pharmacists those activities that would be considered as compounding and those activities that would constitute manufacturing. The law essentially reflected the FDA's prior policies, except for one very important departure. Prior to the law, the FDA had always contended that drugs compounded in the pharmacy pursuant to prescriptions for patients are exempt from the adequate directions for use requirement (misbranding) and CGMP provisions of the FDCA, but not the new drug provision (§ 505). In other words, the FDA held the position that compounded drugs are "new drugs," thus giving the agency the authority to regulate the products if it chose to do so, regardless that the pharmacy was not manufacturing. § 503A took this authority away from the agency. The law defines compounding as "… combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering a drug or bulk drug substance to create a drug." Excluded, however, are such acts as mixing and reconstitution performed in accordance with the manufacturer's directions when performed on receipt of a prescription for a patient.

Under § 503A, a pharmacy is exempt from adequate directions for use, CGMP, and new drug requirements, if the compounded drug product meets the following conditions:

- It is for an individual patient based on the receipt of a valid prescription and compounded by a licensed pharmacist or physician. (This would exclude compounding for another reseller such as a pharmacy or hospital.)
- It is for a 'limited quantity" if prepared in anticipation of receiving a prescription. The amount anticipated must be legitimately based on the established practice history between the prescriber, pharmacy, and patients.
- It is not essentially a copy of a commercially available product, unless compounded only occasionally and not in inordinate amounts. A compounded drug product is not essentially a copy if there is a change made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the commercially available drug.
- It is compounded in compliance with the USP chapters on compounding, using bulk substances that comply with monograph standards, if one exists. If no monograph exists, the drug must be a component of an FDA-approved human drug product. If neither of the previous conditions exists, then it must appear on a list of bulk drug substances developed by the FDA by regulation.

- It is compounded with bulk drugs that are manufactured by an entity registered with the FDA.
- It is compounded with ingredients (other than bulk substances) that comply with USP standards.
- It does not include drugs from an FDA list of items that have been withdrawn or removed from the market because of safety or efficacy.
- It does not include drug products identified by the FDA by regulation as presenting difficulties for compounding because of adversely affecting safety or efficacy.
- The compounder does not distribute more than 5% of the total prescriptions dispensed or distributed by the pharmacy absent a memorandum of understanding (MOU) between the pharmacy's state and the FDA.

The compounding law (§ 503A) appeared to be short-lived, however, because it contained two requirements that the U.S. Supreme Court eventually held were unconstitutional under the First Amendment (*Thompson v. Western States Medical Center*, 535 U.S. 357 (2002)). The first requirement stated that the prescription could not be solicited. The second offending requirement provided that pharmacies and physicians could promote and advertise that they compound, but that they could not advertise or promote the compounding of any particular drug, class of drug, or type of drug. After the Court's decision, uncertainty existed regarding whether all of § 503A was invalidated, because the court of appeals decided that the offending clauses were not severable and the Supreme Court neither agreed nor disagreed with that particular conclusion. This uncertainty created several controversies until the issue was finally decided in the Drug Quality and Security Act (DQSA) of 2013 (discussed later in the chapter).

FDA 2002 Compliance Policy Guide

In reaction to the Supreme Court's decision and on the assumption that § 503A was no longer the law, the FDA drafted a new CPG in May 2002, essentially reinstating by policy many of the provisions in § 503A, less the unconstitutional provisions. In the guidance, the FDA stated that pharmacists have traditionally compounded drugs extemporaneously in reasonable quantities pursuant to a prescription for an individual patient, and that this activity is not the subject of the CPG. However, the FDA continued by noting that it believes an increasing number of pharmacies are engaging in manufacturing and distributing unapproved new drugs clearly outside of traditional pharmacy compounding, and these pharmacies are the subject of this guide.

Demonstrating that it would apply the provisions of the CPG, the FDA sent warning letters in January 2008 to certain pharmacies that compound hormonal replacement products, stating that any claims they make about the safety and efficacy of these products are unsupported and would be considered as false and misleading. The FDA warned that the use of the term "Bio-identical Hormone Replacement Therapy (BHRT)," implying the drugs are identical to hormones made in the body, is misleading. The FDA further warned against compounding products containing estriol, because estriol is not approved by the FDA.

New Drug Issue

As noted, prior to FDAMA, the FDA maintained that a pharmacy-compounded drug is a new drug; however, FDAMA reversed the FDA's position. Once the FDAMA compounding law appeared invalidated, the FDA issued the 2002 CPG and resumed its position that a pharmacy-compounded drug is a new drug. A group of 10 compounding pharmacies brought legal action against the FDA challenging the FDA's policy of considering lawfully compounded drugs as new drugs. In a 2006 federal district court decision (*Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006)), the court agreed with the plaintiffs, finding that compounded drugs are not new drugs and that the nonadvertising provisions are severable, thus leaving FDAMA in effect. The court supported its decision by noting that if compounded drugs were required to undergo the NDA process, patients requiring individually tailored prescription drugs would not be able to receive them due to the cost and time necessary to obtain FDA approval.

On appeal, the Fifth Circuit Court of Appeals voided the district court's decision, but in essence reached a very similar result (*Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008)). The court agreed that the nonadvertising provisions were severable, but held that pharmacy-compounded drugs are new drugs that "are neither uniformly exempt from the new drug approval requirements nor uniformly subject to them." In other words, the court held that compounded drugs are exempt, provided the pharmacy meets all the conditions established in FDAMA. The fifth circuit's decision meant that the FDA was prohibited from treating compounded drugs as new drugs in Louisiana, Mississippi, and Texas (the jurisdiction of the court), but could treat compounded drugs as new drugs in the rest of the country.

Seeking to extend its interpretation of compounded drugs as new drugs outside the fifth circuit, the FDA brought an injunction action against

a pharmacy contending that any medications compounded for animals from bulk substances, even pursuant to a prescription from a veterinarian, are new drugs and violate the FDCA (*United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fla. Sept. 12, 2011)). In denying the injunction, the court noted that the FDA sought to eradicate the line between manufacturing and traditional pharmacy compounding, contrary to congressional intent. Thus, the court concluded that the agency lacked the statutory authority to regulate the traditional pharmacy compounding of animal drugs.

Drug Quality and Security Act of 2013

Uncertainty existed regarding the scope of the FDA's authority over pharmacy compounding, but it did not draw public or Congressional attention until 2012 when a Massachusetts pharmacy (New England Compounding Center [NECC]) compounded and shipped large batches of contaminated sterile injectables to hospital pharmacies, physicians' offices, and other licensed entities. The products killed 64 people and injured more than 700 others, and highlighted the lack of clarity in the law regarding the FDA's authority over large batch compounders.

Congress responded by enacting the DQSA of 2013. Title I of the DQSA, the Compounding Quality Act, reinstated § 503A, striking out the unconstitutional provisions, thus making the law applicable nationwide. The reinstatement of the law also stripped the FDA of its perceived authority to regard any drug product compounded by a pharmacy as a new drug. The FDA issued a compliance guidance in June 2016 explaining its policies regarding the resurrected § 503A and noting that the 2002 CPG was no longer relevant (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf). The agency reemphasized that pharmacies that follow § 503A requirements fall under state regulatory authority and are exempt from federal CGMP, labeling with adequate directions for use, and new drug requirements. It further stated that it expects state boards of pharmacy to continue their oversight and regulation of pharmacy compounding and will cooperate with state authorities when pharmacies violate § 503A. In order to stay abreast of FDA compounding developments, pharmacists can refer to the website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

In addition to reinstating § 503A, the DQSA directly responded to the NECC situation by adding a new category of compounders pursuant to § 503B, under which a compounder of sterile products may voluntarily register to become an "outsourcing facility." An "outsourcing facility" is defined as a facility registered with the FDA that has one geographic location engaged in the compounding of sterile drugs and complies with all § 503B requirements. In general, those requirements include:

- Complying with CGMP requirements (although generally not to the same extent as a manufacturer). See FDA draft compliance guidance at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf.
- Permitting FDA inspections according to a risk-based schedule
- Prohibiting the sale or transfer of compounded products by an entity other than the outsourcing facility
- Compliance with the DQSA labeling requirements for each container
- Meeting certain other conditions such as reporting adverse events and providing the FDA with certain product-compounding information

Section 503B is directed at entities (they need not be pharmacies) compounding and shipping batches of sterile products to other healthcare licensees such as hospitals and clinics not pursuant to patient-specific prescriptions. An entity that only compounds nonsterile drugs does not meet the definition of an outsourcing facility. However, an outsourcing facility may compound nonsterile drugs, provided that it also compounds sterile drugs. Moreover, an outsourcing facility may dispense compounded drug products to individual patients pursuant to a patient-specific prescription.

Registration as an outsourcing facility requires payment of a fee, and the facility's information is then made public on the FDA's website. By registering as an outsourcing facility, the entity agrees to have all its compounded drug products regulated under § 503B, meaning it cannot have a separate area functioning as a § 503A pharmacy. The FDA has issued guidance documents for outsourcing facilities related to defining an outsourcing facility; whether an entity should register as such; registration requirements; fees; electronic drug product reporting requirements; and adverse event reporting requirements. To better assist outsourcing facilities in understanding the applicable laws, policies, and procedures relevant to outsourcing facilities and to assist compounders in deciding whether to register as outsourcing facilities, the FDA in September 2017 issued a publication entitled "Outsourcing Facility Information." This publication and

the CPGs related to compounding can be accessed at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm452240.htm.

The DQSA requires the FDA to establish a mechanism to receive notices of enforcement actions against compounding pharmacies by state boards. Reciprocally, the law requires the FDA to notify state boards when it takes action against a compounder. The law also requires the FDA to publish three drug lists: (1) a list of drugs or categories of drugs with "demonstrable difficulties for compounding," (2) a list of drug products withdrawn or removed from the market, and (3) a list of bulk drug substances for which there is a clinical need that may be used by outsourcing facilities.

Although registration as an outsourcing facility is voluntary, there is considerable incentive to do so. A drug product properly compounded at a registered outsourcing facility will be exempt from meeting the adequate directions for use labeling requirements and will not be considered a new drug. The registered outsourcing facility can legally compound drugs and ship them interstate without receiving prescriptions for individual patients and without quantity limitations. In contrast, an unregistered entity such as a § 503A compounding pharmacy that does so will likely face misbranding, adulteration, and unapproved new drug charges.

Nonetheless, by mid-2017, only about 70 entities had registered as 503B outsourcing facilities, while there are about 7,500 compounding pharmacies. This concerns the FDA and prompted FDA commissioner Scott Gottlieb to issue a statement in September 2017 (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577590.htm). In this statement, the commissioner noted both the patient value of compounded drugs and the patient risks if the drugs are not compounded properly or if they are contaminated. He noted that outsourcing facilities are held to higher regulatory standards, reducing the risk of improperly compounded drugs. Thus, he remarked, the FDA will be taking steps to help and encourage more compounders to register as outsourcing facilities.

The Effect of NECC and DQSA on State Compounding Laws

The NECC tragedy and DQSA prompted many states to enact new pharmacy compounding and outsourcing facility laws and regulations for both sterile and nonsterile compounding. Compounding pharmacies and outsourcing facilities must ensure that they comply with all state requirements, including licensing, recordkeeping, labeling (including BUD), policies and procedures, handling of hazardous drugs (HDs), facilities, equipment, training, and quality assurance. Most states have adopted the USP compounding standards in USP Chapter <795> for nonsterile products and USP Chapter <797> for sterile products (http://www.pewtrusts.org/en/research-and-analysis/reports/2018/02/state-oversight-of-drug-compounding). The USP was discussed in another section of this book, and as noted in that section is recognized in the FDCA as official compendia whose standards have the force of law. Compounding pharmacists must know the USP guidelines and follow them in the event that state requirements are not as comprehensive, especially since § 503A requires that drug products be compounded in compliance with USP standards.

Repackaging Prescription Drug Products

Repackaging is the practice of taking a finished drug product from the manufacturer's container and placing it into a different container, and does not include reconstituting, diluting, mixing, or combining with another ingredient. It does not include the practice of a pharmacy, upon the receipt of a patient-specific prescription, removing a nonsterile drug product from one container and placing it in a different container to dispense directly to the patient. Repackaging is sometimes necessary to meet a patient's needs such as when the patient requires a smaller dose, to reduce waste, to fit a particular device, or to prevent abuse or diversion. Examples of repackaging include transferring tablets and capsules from large containers to unit-dose or blister packs and repackaging bulk creams and lotions into smaller tubes or containers. The FDCA, including sections 503A and 503B, does not exempt repackaged drugs from any of the provisions of the act. Thus, they are subject to the new drug approval, misbranding, adulteration, and other provisions of the act.

In response, the FDA issued a compliance guidance describing the conditions under which it does not intend to take action for repackaging activities by § 503A pharmacies and outsourcing facilities (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434174.pdf). Some of the conditions include: that it is an approved prescription drug product or unapproved prescription drug product that appears on the drug shortage list; the drug product is repackaged by or under the direct supervision of a licensed pharmacist; if repackaged by a pharmacy, it is distributed only after the receipt of a valid prescription for an identified individual patient (this does not apply to outsourcing facilities); and the repackaged drug product is assigned a BUD as described in the guidance, unless evidence

suggests a shorter BUD would be appropriate. Every § 503A pharmacy or outsourcing facility engaging in repackaging should reference this guidance.

Compounding Drug Products That Are Essentially Copies

As listed previously, one of the compounding prohibitions under § 503A of the FDCA is that a pharmacy cannot compound "regularly or in inordinate amounts" any drug products that are "essentially copies" of "commercially available drug products." Excluded are compounded products in which there is a change made for an identified individual patient, which produces for that patient a significant difference between the compounded drug and the commercial drug. Because pharmacies are not subject to the CGMP and pharmacy-compounded drug products are not FDA approved, Congress does not want pharmacies compounding products commercially available. However, pharmacists have been confused in applying this law to practice since the law did not define the terms. To provide clarity, the FDA issued a January 2018 final guidance at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510154.pdf. The guidance provides that a "commercially available drug product" is any marketed drug product, except drug products discontinued or no longer marketed and products appearing on the FDA drug shortage list. A compounded drug product is "essentially a copy" if it has the same active pharmaceutical ingredient (API); the API is the same, similar, or an easily substitutable dosage strength; and the products can be used by the same route of administration. The FDA defines similar dosage strength when the compounded product is within 10% of the commercially available product. "Regularly or in inordinate amounts" is defined as four or fewer prescriptions of "essentially a copy" in a month.

A similar "essentially a copy" requirement exists for a § 503B outsourcing facility. Under the law (§ 503B(a)(5)), an outsourcing facility must not compound "essentially a copy of one or more approved drug products." The definition of "essentially a copy" of an approved drug has two components. Under (§ 503B(d)(2)(A)), a drug is essentially a copy of an approved drug if it is identical or nearly identical to the approved drug or an unapproved nonprescription drug, unless the approved drug appears on the drug shortage list, or as added in the compliance guidance, discontinued drugs. All other compounded drugs are evaluated under § 503B(d)(2)(B), which provides that a compounded drug is "essentially a copy" if a component of the compounded product is also a component of an approved drug, unless there is a change that produces a "clinical difference" for the patient as determined by the practitioner. As it did for § 503A pharmacies, the FDA issued a final compliance guidance in January 2018 to clarify the law for outsourcing facilities (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf.) The guidance provides that a compounded product is identical or nearly identical for the purposes of (§ 503B(d)(2)(A), if all of the following are the same: active ingredients, route of administration, dosage form, dosage strength, and excipients. Unlike with 503A pharmacies, if a compounded drug product is identical or nearly identical, the fact that a prescriber makes a determination of significant or clinical difference does not matter; the product may not be compounded unless there is a drug shortage or if the drug was discontinued.

Both guidance documents contain considerably more detail than provided here, including very helpful flow charts.

Mixing, Diluting, or Repackaging Biologicals

In January 2018, the Agency released a final draft guidance describing the conditions under which the FDA does not intend to take action when a § 503A pharmacy or outsourcing facility mixes, dilutes, or repackages biological products outside the scope of an approved biologics license (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434176.pdf). This is important because the products could not be legally marketed otherwise, since the compounding provisions of the act do not permit these activities in either type of facility. In the guidance, the FDA notes the sensitive nature of biologics to any changes, manipulations, and to storage and handling. Nonetheless, the agency acknowledges that to meet the needs of specific patients, some biological products need to be repackaged in certain manners or mixed or diluted in ways not described in the labeling.

Hospital and Health System Compounding

The FDA issued a draft guidance in 2016 describing how it intends to apply § 503A to drugs compounded by pharmacists or physicians in hospitals or by health system pharmacies for use within the hospital or health system, if these entities are not registered as outsourcing facilities (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496287.pdf). The FDA noted that

§ 503A does not distinguish between stand-alone pharmacies and pharmacies within hospitals and health systems. Thus, they all must equally meet the requirements of the law, including compounding only pursuant to receipt of a prescription or order for an individual patient, or in limited quantities in anticipation of receiving a prescription or order for a patient. However, the guidance provides that the FDA will not take action if the hospital pharmacy compounds drug products without receiving a prescription or order, provided that:

1. The products are distributed only to healthcare entities owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located with a 1 mile radius of the compounding pharmacy;
2. The drugs are only administered within the healthcare facilities to patients within the facilities, pursuant to a prescription or order; and
3. The drugs products meet all § 503A and other applicable FDCA requirements.

Insanitary Conditions at Compounding Facilities

Noting the NECC situation and numerous other prior investigations of serious adverse events associated with contaminated drug products at compounding facilities, the FDA released a draft guidance document in 2016 directed at insanitary conditions (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf). The guidance notes that neither § 503A nor § 503B provides an exemption from § 501(a)(2)(A), which provides that a drug is deemed adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health." The guidance document describes conditions that would be considered insanitary; procedures that compounding facilities should employ to ensure they do not have insanitary conditions and that they are capable of producing sterile products; actions they should take if they identify insanitary conditions at their facilities; and potential FDA regulatory actions if insanitary conditions are not adequately corrected.

Compounding Using Bulk Drug Substances

Pursuant to § 503A, a bulk drug substance that does not meet USP or NF monograph standards or is not a component of an FDA approved drug cannot be used in compounding by a pharmacy or physician unless it appears on a list of bulk drug substances developed by the FDA by regulation. As of August 2018, the FDA has yet to develop this list. However, in a 2017 guidance, the FDA provided that it would not take action against a compounder using a bulk drug substance that is not the subject of a monograph or not a component of an FDA approved drug, provided certain conditions are met (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf). Those conditions include that the substance appears on the 503A Category 1 list on the FDA's website at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf; that the manufacturer of the bulk substance is registered with the FDA; that the bulk substance is accompanied by a valid certificate of analysis (COA); and that all other conditions of § 503A are met.

In contrast to § 503A's bulk drug substance provisions, § 503B provides that an outsourcing facility cannot compound drug products using a bulk drug substance, unless (a) it appears on a list established by the FDA identifying bulk drug substances for which there is a clinical need (Bulk List) or (b) the drug compounded from the bulk drug substance appears on the drug shortage list. Since 2013, the FDA has invited all interested parties to nominate bulk drug substances for inclusion on the 503B bulk substances list. The FDA announced in a January 2017 guidance that until it publishes a finalized 503B Bulk List it would not take action against an outsourcing facility for using a bulk drug substance not on the List, provided the drug compounded (i) appeared on the FDA's drug shortage list within 60 days of distribution and dispensing and (ii) was to fill an order that the outsourcing facility received for the drug while it was on the FDA's drug shortage list (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf). The guidance also provides the agency will not take action if the bulk drug substance does not appear on the Bulk List and is not used to compound a drug on the FDA drug shortage list, provided certain conditions are met, including that the bulk drug substance is listed in Category 1 on the FDA's website of 503B nominated bulk drug substances (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm467374.pdf). In addition, the bulk drug substance must meet the same requirements and conditions discussed for 503A bulk drug substance compounding.

Subsequently, in March 2018, the FDA published a draft guidance describing the policy and process it will

use in evaluating bulk drug substances nominated for the 503B bulk list (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf). The agency stated that it intends to maintain a current list of all bulk drug substances it has evaluated on its website, with separate lists for the substances placed on the 503B Bulks List and those not placed on the list. It emphasized that it will only place those bulk drug substances on the List where a clinical need to compound the drug product has been determined. The draft guidance details how the FDA will interpret clinical need and make such a determination. The agency pointed out that it does not consider supply issues or cost to be within the meaning of clinical need.

Radiopharmaceuticals

Radiopharmaceuticals are radioactive sterile and nonsterile drugs that are used in nuclear medicine to diagnose, monitor, and treat diseases. Radiopharmaceuticals are compounded by a nuclear pharmacy or produced by conventional manufacturers and shipped in multidose containers to an imaging center or hospital for patient administration. The imaging center or hospital's nuclear pharmacy then transfers the radiopharmaceuticals into unit-dose containers and may manipulate the drugs in other ways, such as diluting or pooling them.

There are legal restrictions as to who is permitted to obtain, transport, manipulate, and use radiopharmaceuticals, ranging from the federal Nuclear Regulatory Commission (NRC) to state pharmacy boards that may require permits for those who receive, prepare, repackage, or dispense radiopharmaceuticals. Radiopharmaceuticals that are compounded or repackaged by state licensed nuclear pharmacies are specifically excluded from § 503A, and thus not subject to its exemptions. However, the FDA recognizes that there are circumstances when nuclear pharmacies compound or repackage radiopharmaceuticals to meet patient needs. Therefore, the FDA published a draft guidance in 2016 explaining conditions under which it does not intent to take action when certain violations of the FDCA occur by a nuclear pharmacy not registered as an outsourcing facility (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf).

At the same time, the FDA published a draft guidance directed to § 503B outsourcing facilities that compound and repackage radiopharmaceuticals (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534812.pdf). § 503B applies to the compounding of radiopharmaceuticals, however, not to repackaging drugs (as described earlier). In the guidance, the FDA notes that if the outsourcing facility compounds radiopharmaceuticals it must meet all of the conditions of § 503B. If the entity only repackages, it does not meet the definition of an outsourcing facility. However, if the entity meets the definition of an outsourcing facility and also repackages, it would be eligible for the exemptions provided in § 503B if it complies with the conditions provided in the guidance.

Memorandum of Understanding

§ 503A provides that a compounder cannot distribute more than 5% of its total prescriptions dispensed or distributed by the pharmacy absent a MOU between the pharmacy's state and the FDA. In 2015, the FDA published a draft MOU that would require states to review the compounding records during inspections to determine whether the physician, pharmacist, or pharmacy's interstate distributions are "inordinate" and to notify the FDA (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf). Under the draft MOU, a distribution is deemed "inordinate" if "the number of units of compounded human drug products distributed interstate during any calendar month is equal to or greater than 30% of the number of units of compounded and noncompounded drug products distributed or dispensed both intrastate and interstate during that month." It is unlikely that this definition of inordinate will be the same in the final MOU, as federal legislation (H.R. 244) passed in May 2017 provides language that Congress did not intend "distribute" to include dispensing.

Prescription Requirement for § 503A Pharmacies

In a 2016 final guidance, the FDA reiterated that § 503A permits a drug product to be compounded in two situations: (1) based on the receipt of a valid prescription order for an identified individual patient or (2) in limited quantities before the receipt of a prescription for an identified individual patient (anticipatory compounding) (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf). With regard to anticipatory compounding, interpreted the FDA, the compounded drug products may not be distributed prior to receiving the patient-specific prescription. This interpretation by the FDA would prohibit compounding pharmacies from supplying compounded drugs for "office use" to physicians' offices, clinics, and other healthcare entities.

The FDA's interpretation set off a wave of protest, since compounding for office use is a common practice by many compounding pharmacies and specifically allowed by statute or regulation in some states. However, federal legislation (H.R. 244) was passed in May 2017, stating that Congress intended to include compounding for office use under anticipatory compounding and instructing the FDA to draft a new guidance. Later, in May 2017, a letter signed by 65 members of Congress expressed strong disappointment with the FDA's position on office use and its interpretation that distributing includes dispensing, and urged the agency to reconsider its decision. Despite the language in H.R 244 and the letter from members of Congress, the FDA indicated that its decisions on these issues remain unchanged and conforms to congressional intent. Keep in mind that this limitation is for 503A pharmacies; 503B pharmacies could distribute compounded products for office use.

The guidance also sets forth the FDA's interpretation of "limited quantity" as applied to anticipatory compounding. As set required under § 503A, anticipatory compounding is allowed only if: (1) the compounding is based on a history of the pharmacist or physician receiving prescriptions for the compounded drug; and (2) the prescriptions have been generated solely with an established relationship between the pharmacist or physician and either the patient for whom the prescription will be provided, or the physician or other practitioner who will write the prescription. Therefore, concludes the FDA, a compounder does not exceed a "limited quantity" if: (1) the compounder holds for distribution no more than a 30-day supply of the compounded drug product to fill the prescriptions it has yet to receive; and (2) the amount of the supply is based on the number of valid prescriptions that the compounder has received for identified patients in a 30-day period over the past year. For example, a pharmacy regularly receives prescriptions for patients from prescribers for compounded drug X. The highest number of units of drug X prescribed over a 30-day period during the past year is 500 units. The pharmacy may compound up to 500 units of drug X in advance, holding no more than that amount to fill the prescriptions as they are received.

Other Compounding Issues

Some pharmacies compound herbal products pursuant to prescription. If the product is intended to treat a disease, it could transform the product from a dietary supplement to a drug. If this is the case, the bulk ingredients used must conform to USP standards, and if they do not, it would violate § 503A, possibly making the product misbranded, adulterated, and a new drug.

Occasionally, consumers ask a pharmacist to prepare a nonprescription drug compound for their own use. Such a product might be considered a new drug, adulterated, and misbranded because § 503A requires compounding pursuant to a valid prescription. In many states, such an act would constitute dispensing a prescription drug without a prescription. For example, in an Iowa case, a patient complained to the pharmacist about nasal irritation (*Houck v. Iowa Bd. of Pharmacy Examiners*, 752 N.W.2d 114 (Iowa 2008)). The pharmacist compounded a nasal spray using several nonprescription drug ingredients. The product worsened the patient's condition, and he filed a complaint with the Iowa Board of Pharmacy. The Board found the pharmacist had unlawfully manufactured and dispensed a compounded drug without a prescription, and the court upheld the Board's interpretation that OTC compounded drugs require a prescription.

Patent Issues

Occasionally, compounding by pharmacists can create patent problems with a manufacturer, as did the compounding of minoxidil topical solutions in the 1980s. A legal patent right will supersede a pharmacy's compounding rights. The Upjohn Company first marketed minoxidil in tablet form for oral use as an antihypertensive. A side effect of minoxidil is hair growth, and Upjohn held use patents that enabled the company to label minoxidil exclusively for this purpose. Before Upjohn could market the product for hair growth, however, it had to obtain FDA approval. While Upjohn was waiting for FDA approval to market minoxidil in a topical form, many physicians were already prescribing the drug in topical form for this use, and pharmacists were compounding the prescriptions. Upjohn took no action against the pharmacies at that time even though it held the use patents, because it could not market the drug topically for this purpose anyway and had nothing to gain. Ultimately, the FDA granted Upjohn approval to market the topical form for hair growth and Upjohn began marketing it under the name Rogaine. Upjohn then issued letters to the pharmacies that were compounding minoxidil, warning them that the company would bring legal action unless they stopped the compounding; most pharmacies complied.

The case of minoxidil is somewhat unique in that the use patents for this drug are more enforceable than are those for many other drugs. For example, if a company manufactures a particular drug product in a 25 mg oral tablet and holds a use patent for that product for one indication, it would be difficult or impossible for the company to enforce its use patents if pharmacies compounded the drug in 25 mg oral tablets pursuant

to prescription. The prescribers and pharmacies could simply contend that the drug was being prescribed for indications other than the one patented. Although the company might be able to prove otherwise, it would not likely be worth the company's efforts to attempt to enforce its patents in this situation, especially if the drug is, in fact, used for other indications. In contrast, there is only one clear use for topical minoxidil hair growth.

TAKE-AWAY POINTS

- The FDCA exempts compounding pharmacies from registering as manufacturers when doing so in the regular course of dispensing and selling drugs or devices at retail.
- Since the late 1980s, the FDA has been concerned about the quality and safety of compounded products and has been particularly concerned about compounders who prepare batches of sterile products for sale to other licensed entities.
- FDAMA's § 503A provided considerable clarity as to the distinction between compounding and manufacturing, specifying dispensing situations where a pharmacy would be exempt from registering as a manufacturer and exempt from the adequate direction for use requirement; the CGMP; and the new drug provision. However, the U.S. Supreme Court ruled that two of its clauses were unconstitutional, leading to confusion regarding whether § 503A was completely invalidated.
- After the Supreme Court decision, the FDA published the 2002 CPG, generally adopting by policy the provisions of § 503A.
- Prior to the passage of § 503A, the FDA regarded any drug compounded by a pharmacy as a new drug. Section 503A stripped the FDA of that authority; however, the FDA reasserted this authority in the 2002 CPG after the Supreme Court decision. The Fifth Circuit Court of Appeals ruled that the unconstitutional provisions of § 503A are severable and that drug products compounded pursuant to the exemptions are not new drugs; however, this decision applied only to the jurisdiction of the Fifth Circuit.
- The DQSA of 2013 reinstated the provisions of § 503A (less the unconstitutional provisions) and again stripped the FDA of its authority to declare exempt pharmacy-compounded drugs as new drugs.
- Some of the conditions a § 503A pharmacy must meet to be exempt include:
  - Compounding upon receipt of a prescription for an individual patient
  - Compounding a "limited quantity" in anticipation of receiving a prescription
  - Compounding copies of commercially available products only occasionally and not in inordinate amounts
  - Compounding in accordance to USP standards if in existence
  - Compounding only with FDA approved drugs that have not been withdrawn or removed from the market because of safety and efficacy issues
- The DQSA also created a new category of sterile compounding pharmacies under § 503B known as "outsourcing facilities," a status for which pharmacies could voluntarily register, although an outsourcing facility need not be a pharmacy.
- Sections 503A and 503B do not exempt repackaged drugs from any provisions of the act. However, if pharmacies and outsourcing facilities meet the requirements of the FDA compliance guide, the FDA will not take action against them.
- Although the DQSA does not exempt the mixing, diluting, or repackaging of biologicals, the FDA will not take action against a pharmacy or outsourcing facility that does so and meets the conditions of its compliance guidance.
- The FDA will allow hospital or health system pharmacies to perform some of the functions of outsourcing facilities by compounding drug products without a prescription, provided that certain conditions are met as established in its compliance guide.
- Neither 503A nor 503B allow an exemption to § 501(a)(2)(A) related to insanitary conditions.
- The FDA will not take action against a nuclear pharmacy that compounds or repackages radiopharmaceuticals to meet patient needs in violation of the FDCA, provided the pharmacy meets the conditions in the compliance guide.
- The FDA will permit an outsourcing facility to repackage radiopharmaceuticals, provided it complies with the conditions of the compliance guide.
- The FDA has determined that pharmacies may not supply compounded drugs for "office use" to physician offices and other healthcare entities. However, this determination is controversial.
- The FDA has issued a guidance interpreting "limited quantity" for the purposes of anticipatory compounding.
- A pharmacy that compounds an OTC product not pursuant to prescription would likely be violating the new drug provision of the FDCA, § 503A, and state law.
- Patent rights of a drug manufacturer supersede the rights of a pharmacy to compound that product even pursuant to prescription.

STUDY SCENARIO AND QUESTIONS

Compoundit Pharmacy is near a clinic with three dermatologists, and as a result receives several prescriptions a week for various topical prescription ointments, creams, and gels. Most of the ointments, creams, and gels are available commercially, but Compoundit prefers to compound them because of the greater profits. Compoundit makes large batches of the various topical drugs ahead of time in anticipation of receiving the prescriptions. Other pharmacies in the area also get prescriptions for these topicals but dispense the commercially made products. Compoundit approached these pharmacies, offering to make and sell them the topicals at a lower price than they pay to the manufacturers. The pharmacies agreed to purchase the products from Compoundit. The FDA and board of pharmacy launch an investigation of Compoundit.

1. Is Compoundit acting lawfully pursuant to the provisions of § 503A?
2. Could Compoundit choose to become an outsourcing facility and lawfully perform these activities under § 503B?

Safe Handling of Hazardous Drugs

All healthcare entities, including pharmacies, whether they compound or not that handle HDs, must follow the standards established in USP Chapter <800>. USP 800 published in 2016 will become effective December 1, 2019, and is intended to protect the healthcare worker, the environment, and the patient from the exposure of HDs. The chapter adds to the HD standards contained in USP chapters <795> and <797> and to those from the Occupational Safety and Health Administration (OCSHA).

USP 800 requires entities that handle HDs to maintain at a minimum the following:

- A list of HDs
- Proper facility and engineering controls
- Competent personnel
- Safe work practices
- Proper use of appropriate Personal Protective Equipment (PPE)
- Policies for HD waste segregation and disposal

HDs are defined and identified by the National Institute for Occupational Safety and Health (NIOSH), and the Institute maintains a list of these drugs (available at https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf). The list is reviewed and updated every couple of years, with the 2016 list being reviewed for updates to be finalized in 2018 (see 83 FR 6563). NIOSH divides HDs into three tables, including antineoplastics, non-antineoplastic agents, and drugs with reproductive effects. The definition includes drugs that exhibit one or more of the following characteristics: carcinogenicity, teratogenicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, and structure and toxicity profiles of new drugs that mimic exiting HDs. Each entity must review the NIOSH list and determine the HDs present at its site.

USP 800 does allow in certain situations for entities to make an assessment of risk and to determine alternative containment strategies rather than have to comply with all the containment strategies of the chapter. For example, a community pharmacy that handles tablets or capsules of a HD where the hazard does not pose a significant risk of exposure. The assessment of risk must include at a minimum the type of HD, dosage form, risk of exposure, packaging, and manipulation. Each entity must have a designated person who is qualified and trained to be responsible for developing and implementing HD policies and procedures and complying with the chapter. A free download of chapter <800> is available at http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare.

TAKE-AWAY POINTS

- All healthcare entities, including pharmacies, whether they compound or not that handle HDs, must follow the standards established in USP chapter <800> by December 1, 2019.
- USP 800 requires at a minimum that a healthcare entity handling HDs must maintain a list of HDs, proper facility and engineering controls, competent personnel, safe work practices, proper use of PPEs, and policies for HD waste segregation and disposal.
- NIOSH defines, identifies, and maintains a list of HDs
- When the handling of an HD does not present a significant risk, the entity may make an assessment of risk and determine alternative containment strategies rather than have to comply with all the standards of the chapter.

The Orange Book and Generic Substitution

A discussion of the FDA's publication of the "Orange Book" first requires a background of the developments leading to state generic drug substitution laws.

State Generic Substitution Laws

Today, every state has enacted generic drug substitution laws, expanding the scope of pharmacy practice to allow pharmacists to substitute a generically equivalent drug for the prescribed drug, subject to certain requirements and restrictions. Prior to the early 1970s, few states permitted generic substitution—pharmacists were compelled by law to dispense the brand prescribed by the physician, even if a less expensive and therapeutically equivalent generic product was available. These antisubstitution laws were imposed in the 1940s and 1950s to address abuses by some pharmacists who substituted low-quality and counterfeit drugs for prescribed drugs. However, as more and more generic drugs became approved in the late 1960s and early 1970s, the public's awareness of and demand for lower cost generic drugs correspondingly increased. In addition, the Department of Health, Education and Welfare implemented the Medicaid Maximum Allowable Cost Program in 1974, which encouraged pharmacists to substitute generics by setting upper reimbursement limits on certain multisource drugs. State antisubstitution laws, however, obstructed both patient access to generic drugs and state participation in the Medicaid drug program, prompting state legislative action to allow pharmacists the authority to engage in generic substitutions.

Drug product selection laws vary significantly among states. In "mandatory" substitution states, pharmacists must substitute a less expensive generic drug for the brand name drug, unless the prescriber writes "dispense as written," "brand necessary," or a similar notation on the prescription. In "permissive" substitution states, a pharmacist may choose to substitute if the prescriber issues the prescription in a way that permits substitution. Without the prescriber's permission, either express or tacit, substitution is not allowed in most states, even if the consumer wishes a substitute.

Drug product selection rules apply only when a specific product has been prescribed, usually through the use of a brand name. If a prescription is written generically, the selection is not subject to the drug product selection law because no substitution has occurred. In this situation, the pharmacist may dispense any product in the generic drug class, subject to the ever-present requirement for good professional judgment.

It would constitute misbranding under both state and federal law in most situations if a pharmacist labeled a substituted generic drug with the name of the brand name drug. Other legal violations may also result such as in *Agbogun v. State*, 756 S.W.2d 1 (Tex. Crim. App. 1988), where a pharmacist was found guilty of the misdemeanor offense of deceptive business practices. The record showed that the patient had presented a prescription for Flagyl and that the pharmacist had substituted a generic drug but had labeled the vial with the trade name. The jury apparently disbelieved the pharmacist's explanation that he thought the physician had given him permission to label the bottle of generic tablets inaccurately with the trade name.

Importance of the Orange Book in Generic Substitution

Pharmacists are responsible for ensuring that the substituted generic drug product is bioequivalent to the prescribed product. Bioequivalence basically means that the products display comparable bioavailability (rate and extent of absorption) at the site of action under similar conditions. Despite the enactment of state generic substitution laws, the proliferation of generic drugs in the late 1970s, and pressure from government and consumers to substitute generics, physicians and pharmacists were initially reluctant to substitute because of bioequivalence concerns. To assist healthcare professionals, healthcare entities, and others with this problem, the FDA published *Approved Drug Products with Therapeutic Equivalence Evaluations*. First published in 1979 and republished annually with periodic updates, it quickly became known as the Orange Book because of its orange cover. The Orange Book, whose electronic version can be accessed at the FDA's website at http://www.fda.gov/cder/ob, lists thousands of currently marketed drug products that the FDA has approved as safe and effective. Note that the Orange Book only includes approved drug products; marketed unapproved drug products are not included. The Orange Book is a great resource for healthcare professionals to find out when a drug was approved, when a patent or exclusivity will expire (so as to determine when a generic might be available), and whether generic equivalents exist.

Approved drug products that are "pharmaceutical equivalents" (defined by the FDA as products that contain the same active ingredients and are identical

in strength and are of the same dosage form) are rated in the publication for "therapeutic equivalence." Therapeutic equivalence is defined as pharmaceutical equivalents that can be expected to have the same clinical effect and safety. Pharmaceutical equivalents that are bioequivalent are presumed by the FDA to be therapeutically equivalent. (*Note*: Do not confuse therapeutic equivalence as used in the Orange Book with the separate issue of therapeutic substitution, which refers to substituting different therapeutic agents that may be used for the same condition such as amoxicillin for penicillin.) The issue of whether a generic drug with a different sustained release system than the reference drug should be considered a pharmaceutical equivalent arose in the case of *Pfizer, Inc. v. Shalala*, 1 F. Supp. 2d 38 (D.C. 1998). In this case (which is reported in the case studies section of this chapter), Pfizer challenged the FDA's acceptance of an ANDA from Mylan for a drug with the same active ingredient but a different sustained release system as Pfizer's drug. Pfizer argued that the drugs are not the same dosage form and thus could not be considered as generic equivalents. The court, however, finding for the FDA, concluded that the FDA's interpretation of what constitutes the same dosage form is reasonable.

The FDA uses a two-letter coding system for the therapeutic equivalence evaluations of multisource drug products. The first letter of the code is either an A or a B. Products rated with the first letter A are considered therapeutically equivalent to a reference drug product. Products rated with the first letter B are not considered to be therapeutically equivalent for various reasons, including that they may have documented bioequivalence problems to a reference drug product or there may be a significant potential for such problems and no adequate studies demonstrating bioequivalence. Ratings of B may also indicate that the quality standards are inadequate, or the FDA has insufficient data to determine therapeutic equivalence, or the drug product is still under review. The second letter of the code more specifically describes the dosage form or nature of the product. The list includes:

- AA: Drugs that are available in conventional dosage forms and have no bioequivalence problems
- AB: Drugs identified by the FDA as having actual or potential bioequivalence problems, but which have been resolved by adequate scientific evidence (in contrast, drugs placed in AA, AN, AO, AP, and AT have no known or suspected bioequivalence problems)
- AN: Bioequivalent solutions and powders for aerosolization
- AO: Bioequivalent injectable oil solutions
- AP: Bioequivalent injectable aqueous solutions and some intravenous nonaqueous solutions
- AT: Bioequivalent topical drug with no known bioequivalence problems
- BC: Drugs in extended-release dosage forms with bioequivalence issues
- BD: Active ingredients and dosage forms with documented bioequivalence problems
- BE: Delayed-release oral dosage forms with potential bioequivalence problems
- BN: Products in aerosol nebulizer drug delivery systems, unless proven bioequivalent
- BP: Active ingredients and dosage forms with potential bioequivalence problems
- BR: Suppositories or enemas that deliver drugs for systemic absorption unless proven bioequivalent
- BS: Products having drug standard deficiencies
- BT: Topical drug products with bioequivalence issues
- BX: Products for which the data are insufficient to determine therapeutic equivalence
- B*: Drugs for which no determination of therapeutic equivalence will be made until certain questions have been resolved

Generic drugs marketed after 1984 and approved under an ANDA should all have an A rating, because the Drug Price Competition and Patent Term Restoration Act (PTRA) requires that the generic drug must demonstrate proof of bioequivalence to a reference standard (usually the innovator drug product) before approval. This is confirmed by the fact that the number of drug products in the Orange Book rated as not therapeutically equivalent has decreased dramatically since 1986.

The Orange Book has important implications for pharmacists involved in generic substitution and drug formulary decision-making. For example, if the Orange Book lists four pharmaceutically equivalent drugs, two with a B rating and two with an A rating, the pharmacist may interchange the two drugs with A ratings. However, an interchange of the drugs with B ratings, either with the A-rated drugs or with one another, carries a risk the products will not produce the same clinical effects.

In some situations there may be more than one pharmaceutically equivalent reference drug that have not been determined to be bioequivalent to each other. This situation occurs because the pharmaceutically equivalent products have received approved NDAs and thus must demonstrate bioavailability, not bioequivalence. For these products, the FDA implemented a three-character code such as AB1, AB2, and AB3. If a generic drug product establishes

bioequivalence to one of the reference drugs, it will receive the same three-character code as that reference drug. For example, Adalat CC and Procardia XL are both extended-release nifedipine tablets with approved NDAs, but are not rated as bioequivalent to one another. A generic product to be approved must establish bioequivalence to either Adalat CC or Procardia XL (or both). So, healthcare professionals know which generic products are bioequivalent to which reference drug—Adalat CC is assigned a rating of AB1 and Procardia XL a rating of AB2. Generic products that are bioequivalent to Adalat CC receive a rating of AB1 and those bioequivalent to Procardia XL receive a rating of AB2. Looking at the Orange Book under nifedipine products will reveal generic products rated either AB1 or AB2. AB1-rated drugs are not considered bioequivalent to AB2-rated drugs.

Pharmacists should not switch pharmaceutically equivalent products without consulting the Orange Book if they are not certain of bioequivalence. Switching refers to the practice of substituting a pharmaceutically equivalent product for the drug the patient has been regularly taking. Switching B-rated products and drugs not included in the Orange Book requires a pharmacist's professional care and judgment because the switch could result in significant blood level differences in the patient. If a switch is to occur, pharmacists should consult with the physician and counsel the patient as to the potential risks. (Many state laws require this.) Similarly, formularies should be constructed with an awareness of which drug products carry a B rating or which might not be bioequivalent. Occasionally, the inflexibility of a formulary or the reimbursement mandates of a third-party payer frustrate the exercise of professional judgment.

A pharmacist who substitutes a B-rated drug product for the drug prescribed does not violate the FDCA because the Orange Book is not a mandate; it is merely a guide. The pharmacist might violate state law, however. In most states, substitution or switching is allowed only if the drug is therapeutically equivalent or bioequivalent to the prescribed drug. In addition, switching a B-rated product without evaluating and balancing the clinical risks increases the pharmacist's risk of civil liability should a patient suffer injury.

Narrow Therapeutic Index Drugs

In addition to B-rated and pre-1938 drugs, pharmacists should also recognize the somewhat controversial category of drugs commonly called narrow therapeutic index (NTI) drugs or, as referred to in FDA regulations, narrow therapeutic ratio (NTR) drugs (21 C.F.R. § 320.33(c)). An NTI or NTR drug is defined as one where there is less than a two-fold difference between the median lethal dose and the median effective dose, or where there is less than a two-fold difference between the minimum toxic concentrations and the minimum effective concentrations in the blood. Safe and effective use of these drugs often requires careful titration and patient monitoring. Some examples of NTI drugs listed by the FDA in guidance documents include carbamazepine, clonidine, levothyroxine, lithium, minoxidil, phenytoin, theophylline, and warfarin.

Some drug manufacturers and healthcare providers have expressed concern that the FDA's bioequivalence standards, allowing a range of 80–125% are not precise enough for NTI drugs. These critics have argued for more stringent criteria. Historically, the FDA has rejected such arguments, stating that it has reviewed no clinical data that would warrant narrowing this interval. However, in 2010, the agency reconsidered and presented the issue to an advisory committee that voted nearly unanimously that bioequivalence requirements are not adequate for NTI drugs. Subsequently, the advisory committee met in 2011 and voted that the FDA should adopt new guidelines for NTI drugs including narrowing the potency range to 95–105%, which the agency has adopted.

This means that pharmacists should exercise professional judgment when switching NTI drugs, inform patients of the switch, and alert patients to contact them if they notice any physiological changes. B-rated NTI drugs should not be switched without notifying the prescriber and informing the patient. Pharmacists also must be aware of state laws that may restrict the substitution of some of these products.

Substitution of Biosimilar Biologics

In addition to drug product substitution, pharmacists must also be knowledgeable about biologic product substitution. Although biologics are generally discussed in another section of this book, further discussion is warranted here as related to product substitution. In 2010, the Biologics Price Competition and Innovation Act (BPCIA) created a regulatory framework to facilitate the approval of generic biologics, also called biosimilars.

Approval and marketing of biosimilars creates the issue of whether a biosimilar can be substituted by a pharmacist for the prescribed reference drug or even for another biosimilar. Since biosimilars are not pharmaceutically equivalent products like generic drugs, establishing bioequivalence is not possible. Therefore, the law defines biosimilarity as meaning the product is "highly similar" to the reference product with

no clinically meaningful differences in safety, purity, and potency. However, in order for a biosimilar to be deemed interchangeable, it must meet additional requirements pursuant to the law. In part, this means that the applicant must establish that the biosimilar is expected to produce the same clinical result as the reference product in any given patient without any greater risk. The FDA assures healthcare professionals that interchangeable biologics can be switched back and forth in patients without any risk.

To guide healthcare professionals in evaluating biologics, the FDA electronically publishes the "Purple Book" (https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm). The Purple Book includes the date a biological product was licensed and whether the product has been determined to be biosimilar to (noted with a "B") or interchangeable with (noted with an "I") a reference biological product.

The BPCIA provides that if the FDA determines that a biosimilar is interchangeable, it may be substituted for the reference product without the intervention of the prescriber. If the product is approved as biosimilar but not interchangeable, the FDA expects that the biosimilar can be specifically prescribed by the healthcare professional but cannot be substituted for a reference product by the pharmacist. As with generic drug substitution, however, pharmacists must look to their state laws and regulations to determine the requirements in which they may substitute a biosimilar for the prescribed reference biologic. As of July 2017, 35 states have enacted statutes with varying provisions and several states have had bills introduced (https://comm.ncsl.org/productfiles/93301324/NCSL-Laws_Biologics_Biosimilars.pdf). State laws enacted to date generally permit substitution of an interchangeable biosimilar, provided the prescriber has either authorized or not prohibited substitution and that the pharmacy notified or communicated with the prescriber the substitution.

TAKE-AWAY POINTS

- Prompted by the increased availability of generic drugs and Medicaid, every state has passed laws permitting pharmacists to substitute a generic drug product for the drug product prescribed.
- State drug product substitution laws vary from mandatory in some states to permissive in others.
- The FDA first published the Orange Book in 1979 as a guide to healthcare professionals because of concerns about the bioequivalence of generic drugs.
- The FDA's Orange Book rates pharmaceutically equivalent drugs on the basis of therapeutic equivalence using a two-letter coding system, with the first letter either an A or a B.
- Pharmacists should know whether pharmaceutically equivalent drugs are therapeutically equivalent before switching a patient from one drug to another.
- Substituting or switching a patient (without prescriber authorization) to a drug not therapeutically equivalent requires the exercise of professional judgment.
- NTI drugs are those with a narrow window between their median toxic or lethal dose and their median effective dose.
- Pharmacists should always exercise particular caution and professional judgment when substituting or switching narrow therapeutic drugs that are B rated.
- The BPCIA created a regulatory framework to facilitate the approval of generic biologics, also called biosimilars.
- Biosimilarity means the product is "highly similar" to the reference product with no clinically meaningful differences in safety, purity, and potency.
- In order for a biosimilar to be interchangeable, the applicant must establish that the biosimilar is expected to produce the same clinical result as the reference product in any given patient without any greater risk.
- To guide healthcare professionals in evaluating biologics, the FDA electronically publishes the "Purple Book," where biosimilars are noted with a "B" and, if interchangeable, with an "I".

STUDY SCENARIO AND QUESTIONS

Sally, a pharmacist at SuperClinic Pharmacy, received a prescription from a patient, Mr. Lee, for Menton (fictional drug product). Mr. Lee asked if there was a less expensive generic drug available because he had to pay for his medications personally. Sally knew that there was a generic product available but that it had a B rating to Menton in the FDA's Orange Book. Sally was uncertain whether to dispense the generic or not.

1. What does it mean that Menton has a B rating?
2. How is it possible that the generic is not bioequivalent to Menton?
3. How should the fact that the generic is B rated affect Sally's substitution decision if Mr. Lee has previously been taking Menton? Explain how Sally should proceed.
4. How should the fact that the generic is B rated affect Sally's substitution decision if Mr. Lee has not previously taken the drug?
5. Explain whether substituting the generic for Menton would violate federal law or the law in your state. If so, how could Sally legally substitute the drugs?
6. If a substitution is made, what should Sally tell the patient during counseling?

Drug Supply Chain Security

The drug supply chain refers to the system, beginning with the manufacturing process of a drug product with bulk ingredients; to the distribution process incorporating wholesalers, repackagers, warehouses, transportation, and pharmacies; and to the dispensing of the drug product by the pharmacy to the patient. This complex drug supply chain offers the opportunity at numerous stages for drug product diversion and to introduce counterfeit drug products as well as adulterated and/or misbranded drug products with potentially devastating results. The FDA has several documented instances of such drug products finding their way into the inventory of pharmacies. Ensuring the security of the supply chain, of course, is a major concern of Congress, the FDA, and the public. With this objective, two significant amendments have been made to the FDCA: the PDMA of 1987 and the Drug Supply Chain Security Act (DSCSA) of 2013.

Prescription Drug Marketing Act of 1987

Enacted in 1987 (P.L. 100-293), the PDMA amends the FDCA to:

- Require states to license wholesale distributors of prescription drugs
- Ban the reimportation of prescription drugs, except by the manufacturer or for emergency use
- Ban the sale, trade, or purchase of drug samples
- Mandate storage, handling, and recordkeeping requirements for drug samples
- Ban the trafficking in or counterfeiting of drug coupons
- Prohibit the resale of prescription drugs purchased by hospitals or healthcare facilities, with certain exceptions

The PDMA was passed after 2 years of congressional hearings, during which it was established that many prescription drug products were being misbranded and adulterated because they were being diverted from the normal stream of distribution. Congress concluded that the U.S. public could no longer purchase prescription drugs with the certainty that the products were safe and effective unless legislation was enacted. The FDA issued final regulations, implementing the PDMA in 1999 (64 Fed. Reg. 67720).

Regulation of Prescription Drug Samples

Congressional investigators discovered that drug manufacturers' representatives commonly left large quantities of samples at hospitals, physicians' offices, clinics, and other locations. They kept few records of distribution, and there was no quality control for the storage of these samples. This situation was exacerbated by individuals who gathered up the samples, combined them into stock bottles, relabeled the bottles, and sold them to community and hospital pharmacies. The pharmacies then dispensed and sold the samples to patients. Often, the drugs had been improperly stored under hot or unsanitary conditions, were improperly labeled, and mixed with other drug lots. The consumer had no assurance that the drugs were unadulterated or labeled properly. To prevent these abuses, the PDMA prohibits the sale, purchase, or trade of samples. The same restrictions apply to coupons used to redeem the drug at no cost or at a reduced cost.

A sample is defined as a unit of drug intended not to be sold but rather to promote the sale of the drug. Starter packs distributed by manufacturers free to pharmacies are not considered samples because they are not labeled as such and could be sold. Samples from manufacturers and distributors may be distributed only to practitioners licensed to prescribe or to pharmacies of hospitals or healthcare entities (i.e., organizations that provide diagnostic, medical, surgical, or dental treatment but do not include a retail pharmacy) at the written request of the prescriber on a form that includes the information specified by law. The practitioner must make the request each time; a standing request is not acceptable. If the distribution is by mail or common carrier, the recipient must execute a written receipt for the sample on delivery and the receipt must be returned to the manufacturer

or authorized distributor. The manufacturer and distributor must store the samples under proper conditions. They also must keep annual inventories of samples in the possession of company representatives.

Proposed regulations by the FDA (59 Fed. Reg. 11842, March 14, 1994) emphasized that retail pharmacies are barred from receiving any sample prescription drug, and provided that the mere presence of any sample prescription drug in a retail pharmacy shall be considered evidence that the sample was obtained illegally. Although this strong language was not included in the final regulations, the final regulations clearly do not allow retail pharmacies to receive samples (59 Fed. Reg. 67720, 1999). The pharmacy of a hospital or healthcare entity may receive samples at the request of a licensed practitioner, provided there is a receipt containing:

- The name and address of the requesting prescriber
- The name and address of the hospital or healthcare entity designated to receive the drug sample
- The name, address, title, and signature of the person acknowledging delivery of the drug sample
- The proprietary or established name and strength of the drug sample
- The quantity and lot or control number
- The date of delivery

Purchases and Resales by Hospitals and Healthcare Entities

Diversionary markets did not involve only drug samples. Congressional investigators discovered that prescription drugs were diverted when hospitals and healthcare entities resold their excess purchases. Because of their nonprofit status, cooperative bidding practices, and restrictive formularies, hospitals, health maintenance organizations, and other healthcare entities often are able to purchase drugs at prices much lower than community pharmacies pay for the same drugs. Some healthcare entities were reselling their purchases at a markup to brokers, retail pharmacies, and even wholesalers. This practice created misbranding and adulteration problems because the drugs were often improperly stored under unsanitary conditions in garages and automobile trunks for long periods of time. In addition, some drugs were repackaged from large containers into smaller, improperly labeled containers under unsanitary conditions. Such schemes also led to unfair competition because pharmacies that purchased the drugs in the diversionary market obtained a price advantage over those that did not participate.

In an attempt to stop this diversionary market, the PDMA prohibits the sale, purchase, or trade (or offer to do so) of prescription drugs that have been purchased by a hospital, healthcare entity, or charitable organization. Very important exceptions to this general rule include:

- A hospital's purchases from a group purchasing organization or from other member hospitals for its own use
- Sales or purchases to nonprofit affiliates
- Sales or purchases among hospitals or healthcare entities under common control
- Sales or purchases for emergency medical reasons (e.g., transfers allowed between healthcare entities or from a healthcare entity to a community pharmacy to alleviate a temporary shortage of a prescription drug)
- Selling or dispensing prescription drugs pursuant to prescriptions

Product Returns

Shortly after passage of the law, there was some confusion regarding whether hospitals and healthcare entities could legally return mistakenly ordered and outdated prescription drug products to wholesalers and manufacturers or whether these transactions would constitute a sale or trade. After considerable debate, the FDA agreed to permit legitimate returns, provided that the drugs are properly stored and handled and proper records are kept (21 C.F.R. part 205).

Wholesale Distributors

Under the PDMA, all persons engaged in the wholesale distribution of prescription drugs must be licensed by the state in accordance with prescribed guidelines. Wholesale distribution is defined as distribution to anyone other than the consumer. The intent of this provision is to prevent individuals who can obtain drugs at lower prices from reselling those drugs unless they are licensed as a wholesaler. Through licensure, the states can ensure that those functioning as wholesalers meet the required standards. In 1990, the FDA established uniform standards that wholesale distributors of prescription drugs must meet to be licensed (21 C.F.R. part 205); some of these standards were subsequently amended by the 1999 regulations. Because of the counterfeit drug problem (discussed next) and the threat of terrorism, some associations have argued that state regulation does not work for interstate wholesalers and that the FDA should assume the licensure of wholesalers.

Pedigrees

In an effort to reduce the risk of diverted, unapproved, and/or counterfeit drugs being introduced into the supply chain, the PDMA granted the FDA the authority

to require wholesalers that are not manufacturers and that are not authorized by a manufacturer of the drug to maintain a record that identifies each prior sale, purchase, or trade of the drugs they receive and distribute. This type of record is generally called a "pedigree" because it contains information on each transaction changing the ownership of the drug. Wholesalers not authorized by a manufacturer are generally called secondary wholesalers. Secondary wholesalers are a legal and important component of the drug distribution system and far outnumber authorized wholesalers. Although the three largest wholesalers sell 90% of all drugs in the United States and buy primarily from manufacturers, there are over 7,000 smaller secondary wholesalers that buy drugs from several sources and sell to several difference sources, including to the three largest wholesalers. The PDMA limited the pedigree requirement to secondary wholesalers because, at the time, Congress found that most of the problems of counterfeiting and diversion occurred in the secondary market.

Interpreting what the PDMA meant by "each prior sale," the FDA issued a final regulation to implement the pedigree requirement in 1999 (64 Fed. Reg. 67720), requiring each secondary wholesaler to receive and distribute a pedigree that includes a record of ownership back to the "original" manufacturer. The FDA, however, then delayed implementation because of concerns from the wholesale industry regarding the cost and burden of maintaining a paper pedigree on each drug. Now, however, electronic technologies exist such as radio frequency identification (RFID) to make pedigrees much more workable.

The FDA announced in June 2006 that the regulation would no longer be delayed and would become effective December 1, 2006 (71 Fed. Reg. 34249). Subsequently, the FDA published a CPG intended to clarify how the FDA plans to prioritize enforcement of the pedigree requirements. However, on November 30, 2006, one day before the regulation's effective date, a federal district court issued a preliminary injunction against the DHHS preventing the regulation's implementation, and the court of appeals affirmed the decision in 2008 (*RxUSA Wholesale, Inc., et al. v. DHHS*, 467 F. Supp. 2d 285 (E.D.N.Y. 2006); aff'd. 285 Fed. Appx. 809 (C.A.2 (N.Y.) 2008)). The court agreed with the secondary wholesaler plaintiffs that if the regulation became effective, they would suffer irreparable harm and that the PDMA pedigree requirement likely violates the U.S. Constitution's equal protection clause. The reason for the court's ruling was that the regulation (in conformance with the PDMA) requires only secondary wholesalers to have records tracing the drug back to the original manufacturer. Secondary wholesalers generally purchase from authorized wholesalers, who do not have to keep these records and thus would not have them to pass on to the secondary wholesalers. This would mean that the secondary wholesalers could not obtain a record of ownership from the original manufacturer, would be powerless to comply with the regulation, and would go out of business as a result. Both the district and appellate courts found that the PDMA does not specifically require that the pedigree must extend back to the original manufacturer, but rather only to the last authorized distributor. Based on the court decisions, the FDA issued a proposed regulation in July 2011 (never finalized) that would, instead, require secondary wholesalers to identify the last authorized distributor (76 Fed. Reg. 41434). The FDA acknowledged that a real solution to the plight of the secondary wholesalers would require statutory remedies from Congress.

For these reasons, Congress included in the 2007 FDAAA a mandate that the FDA, by March 2010, prioritize and develop standards to identify, authenticate, and track and trace prescription drugs; develop a standard numerical identifier to be applied to the drug product by the manufacturer; and utilize promising technologies such as RFID, nanotechnology, and encryption. In 2010, the FDA issued a final guidance document announcing the development of standardized numerical identifiers (SNIs) for prescription drug packages as its initial step in complying with the FDAAA mandate (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf). The package level is defined as the smallest unit sold by the manufacturer to a dispenser. The FDA recommends that the SNI on the package should be the National Drug Code combined with the manufacturer's unique serial number for the package (termed a serialized NDA or sNDA).

The FDA Safety and Innovation Act of 2012 expanded the FDA's authority regarding manufacturer registration, facility inspection, and importation. The law was to have included the standards for a national pedigree system; however, disagreement among legislators, manufacturers, wholesalers, and pharmacies caused it to be deleted.

Drug Supply Chain Security Act of 2013

Because of the lack of a federal pedigree program, some states enacted their own pedigree laws and other states planned to follow. Needless to say, a patchwork of state pedigree laws was hardly desirable. Congress preempted these state laws by passing the DSCSA in 2013, which is Title II of the DQSA (remember that

Title I of the DQSA is the Compounding Quality Act). In October 2014, the FDA issued a guidance document that emphasized the preemption effect on state pedigree laws (http://www.regulations.gov/#!documentDetail;D=FDA-2014-D-1411-0002).

The DSCSA applies to "trading partners" within the prescription drug supply chain. Trading partners include five types of entities: manufacturers, wholesalers, repackagers, third-party logistics providers (3PLs), and dispensers (pharmacies). In 2017, the FDA issued a guidance document to assist these entities and state and local governments better understand the DSCSA requirements applicable to these entities and clarify whether they are engaged in activities requiring licensure and annual reporting (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM572252.pdf).

Trading partners must have systems in place to quarantine, investigate, and notify the FDA and certain other partners of "suspect" and "illegitimate" prescription drug products (e.g., counterfeit, diverted, stolen, and adulterated or unfit so as to cause serious adverse health consequences) not later than 24 hours after making the determination. The FDA issued guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf) in 2014 and reissued in 2016 for the purposes of:

- Identifying specific scenarios that could significantly increase the risk of a product entering the supply chain
- Providing recommendations on how to identify that the product might be suspect
- Setting forth a notification process

Draft guidance issued in March 2018 provides definitions for "suspect products" and "illegitimate products" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm598737.pdf).

The DSCSA requires that by November 2023 a full system electronic, interoperable product track and trace (pedigree) system be implemented for prescription drugs for human use. There are several exceptions, including homeopathic drugs, compounded drugs, and radioactive drugs. Product tracing information, which includes transaction information, history, and statement, must be passed, received, and maintained for 6 years by each supply chain partner. The law allows for a phase-in period. By January 1, 2015, manufacturers must pass product tracing information to subsequent purchasers. Repackagers and wholesalers must receive the product tracing information and pass the data on to subsequent purchasers. By July 15, 2015 (extended by the FDA to March 1, 2016), dispensers cannot receive a prescription drug product unless the prior owner provided product tracing information. The dispensers must provide the product tracing information to subsequent purchasers, except for patients and the exceptions (noted later). In November 2014, the FDA issued a draft guidance providing that nearly any method—paper or electronic—of passing product tracing information is acceptable, provided that it includes all the required information (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm424895.pdf). In March 2018, the FDA issued draft guidance for the purpose of elaborating on the standards for interoperable exchange of product tracing information (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm598734.pdf). The guidance is intended to assist trading partners by providing recommendations for standardizing the data of the product tracing information and documentation practices a trading partner can use to meet its product tracing obligations.

The product tracing information requirements apply to transactions where the prescription drug products change ownership. Important exceptions for pharmacies include:

- Transfer from one pharmacy to another to fulfill a specific patient need such as filling a prescription
- Distribution in a minimal quantity by a pharmacy to a practitioner for office use
- Distribution pursuant to a sale or merger of a pharmacy
- Distribution of drug/device combination products
- Distribution for emergency medical reasons
- Product returns

In 2017, the FDA added transactions with first responders as another exception to the requirement of exchanging tracing information (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM488240.pdf.). Provided the conditions established in the guidance are met, the FDA will not take action against a dispenser (or any trading partner) who transfers a product directly to a first responder. Nor will the FDA take any action against a first responder, even though that first responder is not licensed as a trading partner. Conditions for the exemption include that the dispenser captures and maintains the product tracing information for not less than 6 years, and provides this information to the first responder or Secretary, if requested, not later than two business days after

receiving the request or such other reasonable time as determined by the Secretary.

The law requires that manufacturers must affix a unique product identifier (UPI; most likely the FDA's suggested SNI) to each individual package and homogenous case by November 2017; however, the FDA has extended enforcement to November 2018 (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM565272.pdf). By November 2018, repackagers must do the same. By 2019, wholesalers can only accept products containing the UPI and by 2020, dispensers can only accept products containing the UPI. By November 2023, all supply chain partners will be required to electronically track and trace products using the UPI. Before these track and trace requirements can be implemented, the law requires that DHHS contract with an independent consulting firm to assess the feasibility of compliance by pharmacies with 25 or fewer full-time employees.

In addition, the law establishes uniform national licensing standards for wholesalers and 3PLs (companies that do not own but receive, store, and ship prescription drugs and devices). Although states will continue to license wholesalers and 3PLs, they must apply the federal standards to do so. Wholesalers and 3PLs are then required to report their licensing status and contact information to the FDA, which is then made available in a public database. In December 2014, the FDA issued a draft guidance to assist wholesalers and 3PLs to comply with the DSCSA reporting requirements and is in the process of drafting regulations (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM426126.pdf).

Importation of Prescription Drugs for Personal Use

Generally speaking, the importation of prescription drugs from another country is illegal, because the FDA has likely not approved the drug or else not approved the manufacturer to manufacture the drug. The PDMA does allow the reimportation of prescription drugs, but only by the original manufacturer or for emergency use. The Medicare Prescription Drug, Improvement, and Modernization Act (MMA) allows the Secretary of DHHS to promulgate regulations that facilitate the wholesale importation of prescription medications from Canada. The secretary may only do so, however, if the secretary can certify the program would pose no additional risk to public health or safety and would significantly reduce cost. To date, the secretary has refused to recognize any certification.

Under a compassionate use policy in place for several years, the FDA has permitted the personal importation or shipment of generally not more than a 3-month supply of drugs. In determining whether to allow the importation, the FDA will consider a permissive policy if the drugs are not approved in the United States and are used for the treatment of a serious condition for which no satisfactory treatment is available in this country. The drug must not represent an unreasonable risk and the patient seeking to import the drug must provide the name of the licensed U.S. physician responsible for treating the patient with the unapproved drug or evidence that it is a continuation of treatment in a foreign country. The patient must also attest in writing that the product is for the patient's own use and not for commercialization or promotion (http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179266.htm).

Under a provision in the Department of Homeland Security Appropriations Act of 2007, however, an individual patient may import an FDA-approved prescription drug from Canada (P.L. No. 109-295). The exemption applies only to individuals transporting the drug on their person in a quantity not to exceed a 90-day supply. Moreover, the drug may not be a controlled substance or biological product.

The Controlled Substances Act and regulations do allow for a personal use exemption for controlled substances, regardless of the country. The exemption only allows for a total combined quantity of 50 dosage units that must be transported personally, not shipped, across the border (21 U.S.C. § 956, 21 C.F.R. § 1301.26). The drug must be in the original, dispensed container and must be declared at customs. The 50 dosage unit limitation does not apply to controlled substances lawfully dispensed in the United States by a Drug Enforcement Administration registrant.

Nonetheless, many U.S. patients have for years crossed the borders of Canada and Mexico to have their prescriptions dispensed in those countries at lower prices, and the FDA has generally not taken any action. In recent years, Internet as well as brick and mortar businesses have offered patients nationwide the option of purchasing their medications through Canadian pharmacies. (Canada has become the country of choice because of easier availability of drugs and fewer fears of counterfeiting, adulteration, and misbranding.)

Some states and cities have even authorized or proposed prescription benefit plans that allow patients to purchase the drugs from Canada. Vermont filed a petition with the FDA to allow its state employee benefit plan to import prescription medications, but the FDA rejected the petition. Vermont then sued DHHS and the FDA contending that the MMA was unconstitutional because it delegated Congressional authority to approve importation to the secretary. Vermont also

asked for the prompt issuance of regulations allowing for importation. The court found that the Vermont plan violates the FDCA and that the MMA establishes an "intelligible principle" directing the secretary to certify safety and costs, and as such, the delegation is not illegal (*State of Vermont v. Leavitt*, 405 F. Supp. 2d 466 (D. Vt., Sept. 19, 2005)). Maine enacted a law in 2013 that allows its residents to obtain prescription drugs by mail from pharmacies in Canada and the United Commonwealth. However, a federal district court ruled in 2015 that the law is preempted by the FDCA (*Ouellette v. Mills*, 2015 WL 751760 (D. Me.)).

The FDA has staunchly maintained that although it sympathizes with consumer and local government efforts to obtain drugs at lower prices, the practice of importing prescription drugs from other countries for U.S. patients violates the PDMA (21 U.S.C. § 381(d) (1)). In *United States v. Rx Depot, Inc.*, 290 F. Supp. 2d 1238 (N.D. Okla. 2003), the FDA brought an injunction action against a company engaged in this practice. The defendant, Rx Depot, operated stores throughout the United States and solicited patients to mail, fax, or deliver their prescriptions to one of its stores. Rx Depot would then transmit the prescription and a medical history form it required the patient to provide to a participating pharmacy in Canada. A Canadian doctor would rewrite the prescription and the Canadian pharmacy would fill and ship it directly to the patient in the United States. Rx Depot would receive a 10–12% commission for each sale. The court concluded that it was sympathetic to patients who cannot afford prescription drugs at U.S. prices, but that Rx Depot was violating the law and thus granted the FDA's motion for an injunction, requiring that the defendant cease its operations.

The FDA has promised enforcement action against businesses engaged in these activities because of public health concerns. The agency maintains that most drugs sold outside the United States, including in Canada, have not received FDA approval. Many drugs produced for foreign markets are made by firms that have not applied for FDA approval. Even if a manufacturer has FDA approval for a particular drug in this country, the FDA contends that the version produced for other markets usually does not meet all the requirements for U.S. approval. As a result, the agency is greatly concerned that foreign products risk being adulterated or misbranded as well as counterfeited. After a 1 year investigation, a DHHS Task Force issued a report in December 2004 finding that drug reimportation presents significant risks (http://www.hhs.gov/importtaskforce).

Penalties

The penalty provision in the PDMA is extensive and specific. There are several different penalties, including up to 10 years in prison, a $250,000 fine, or both, for first offenses.

TAKE-AWAY POINTS

- The PDMA requires that prescription drug samples be distributed only to prescribers or pharmacies of hospitals or healthcare entities, and subject to certain requirements.
- The PDMA prohibits the sale, purchase, or trade of prescription drugs purchased by a hospital, healthcare entity, or charitable organization, with certain exceptions.
- Wholesalers must be licensed by the state in which they are located.
- The PDMA contained a requirement that unauthorized wholesalers obtain a pedigree with the drug product. However, the FDA's attempt to implement the requirement by regulation was enjoined by a federal court as being unconstitutional.
- The FDAAA required the FDA to develop standards to identify, authenticate, and track and trace (pedigree) prescription drugs.
- The DSCSA requires that trading partners have systems in place to quarantine, investigate, and notify the FDA and certain trading partners of suspect products by January 1, 2015, and requires that a full system electronic, interoperable track and trace system be implemented by November 2023.
- The DSCSA requires that trading partners, including pharmacies, must receive and transfer transaction data which includes the transaction information, history, and statement
- Manufacturers must affix a uniform product identifier (UPI) on each individual package and homogenous case by November 2018
- Pharmacies are exempt from transferring transaction information in seven specific situations
- In general, the importation of prescription drugs is illegal; however, persons may import a limited amount for personal use if certain conditions are met.
- Courts have ruled that state and local government actions to obtain drugs from Canada or other countries for their employee benefit plans violate federal law.
- U.S. pharmacies or other entities assisting patients in purchasing prescription drugs from other countries could face prosecution by the FDA.

STUDY SCENARIOS AND QUESTIONS

1. Through the power of its purchasing cooperative and its nonprofit status, Mercy Hospital's pharmacy is able to purchase prescription drugs at much lower prices than community pharmacies. The director of the pharmacy decided to purchase more inventory than the pharmacy needed and to sell the excess inventory to community pharmacies. The hospital benefited by making extra profit and the pharmacies benefited by purchasing the drugs at less than their direct cost from the manufacturer. Explain if this activity is legal and why. What if, instead of Mercy Hospital purchasing and reselling the drugs, it was a chain pharmacy? Would your answer change and why?
2. Blueway Pharmacy and Redway Pharmacy commonly sell one another prescription drug products when one or the other is out of stock. They also sell prescription drug products to a local physician for his office use and to the local ambulance service. Explain whether Blueway and Redway must transmit transaction data in these situations.
3. Tom and Mary are a middle-aged couple who pay out of pocket nearly $2,000 per month for prescription drugs in your pharmacy. One of their friends told them that they could buy the drugs in Canada for about half that price. Tom and Mary ask you if they could legally buy the drugs in Canada. If so, they wonder how they could do this and ask if you could get the drugs for them and their friends. Provide Tom and Mary with accurate information on this subject.

Inspections Under the Federal Food, Drug, and Cosmetic Act

The FDA does not routinely inspect pharmacies. Section 704 of the FDCA states that FDA inspectors may inspect facilities where drugs are held at reasonable times, within reasonable limits, and in a reasonable manner. However, § 704 exempts from FDA inspection authority pharmacies that regularly dispense prescriptions and that do not manufacture, prepare, or compound drugs or devices for sale other than in the regular course of their retail business. Nonetheless, the agency has always assumed it has the authority to inspect pharmacies, especially when it has reason to believe that the pharmacy may be engaging in manufacturing or repackaging activities, and has often done so.

Subsequent to issuing the 2002 compounding CPG, the jurisdiction of the FDA to inspect a pharmacy for compounding violations was challenged in the case of *Wedgewood Village Pharmacy, Inc. v. U.S.*, 421 F.3d 263 (2005). Based on a number of concerns, including that the pharmacy was compounding drugs that were essentially copies of commercially available products and using commercial-scale manufacturing equipment, the FDA obtained a warrant and commenced inspection. After 3 days of inspection, however, the pharmacy filed a motion to quash the warrant on the basis that the FDA had no jurisdiction over state-licensed pharmacies as specified in the FDCA. Thus, argued the pharmacy, pharmacies are exempt from FDA inspection. Ruling for the FDA, however, the court stated that Congress intended that the FDA be granted the authority to generally inspect pharmacies in order to determine if the exemption applies. Otherwise, the FDA would have to rely on the representations of the pharmacies and essentially be powerless to enforce the law. If the FDA has probable cause to believe the pharmacy is manufacturing, the FDA can extend the search to the pharmacy's records.

FDA agents do not need a warrant under the statute but merely must show their credentials and a notice of inspection. They do not even need to state the reason for the inspection. The U.S. Supreme Court has never considered the constitutionality of the warrantless search statute; however, a pharmacist would be wise not to refuse an agent without a warrant. Refusing entry to FDA inspectors could result in a penalty of up to 1 year in prison, a $1,000 fine, or both (FDCA § 301(f) and § 303(a)).

TAKE-AWAY POINTS

- The FDCA exempts pharmacies from FDA inspection authority when they do not manufacture, prepare, or compound drugs or devices other than in the regular course of their retail business.
- The courts have held that the FDA can inspect pharmacies based on the probable cause that they might be in violation of the law in order to determine that fact.
- FDA agents do not need a warrant to search.

STUDY SCENARIO AND QUESTION

Compoundit is a retail pharmacy that specializes in compounding prescription drugs. The local hospital purchases a certain sterile injectable from Compoundit. Two patients suffered injury allegedly because of contamination of the product supplied by Compoundit and the FDA sent an inspector to Compoundit to investigate. Compoundit refused to allow the inspector access stating that the FDA had no authority to inspect and that the agent did not have a warrant. Discuss whether Compoundit can legally refuse the FDA access.

Related Laws to the FDCA

Laws important to pharmacy practice and related to the FDCA include those involving the use of alcohol and those establishing requirements for drug containers.

Use of Alcohol in Pharmacy Practice

Pharmacists handle several kinds of alcohol, depending on their practice setting. These include denatured alcohols (rubbing alcohol and alcohols used in compounding external medications), ethyl alcohols (used in compounding internal and external medications, flavoring agents, etc.), and isopropyl alcohol. Tax-paid ethyl alcohol is the beverage liquor sold in such retail outlets as liquor stores, grocery stores, and pharmacies. Anyone selling federally taxed alcohol at retail must conform to the licensing and tax requirements established by the Bureau of Alcohol, Tobacco, Firearms and Explosives and the Internal Revenue Service. Community pharmacies that use alcohol to compound prescriptions commonly use tax-paid ethyl alcohol, usually 190-proof grain alcohol, purchased from an authorized retail or wholesale outlet.

In contrast, some entities are entitled to use 190-proof ethyl alcohol, which is not taxed by the federal government (called tax-free alcohol). Tax-free alcohol may be used by the following entities for the following purposes (27 C.F.R. part 22):

- State or political subdivisions for scientific and mechanical purposes
- Educational institutions for scientific and mechanical purposes
- Laboratories for scientific research
- Hospitals, blood banks, and sanitariums for scientific, mechanical, and medicinal purposes, and in the treatment of patients
- Pathology laboratories in connection with hospitals and sanitariums for scientific, mechanical, and medicinal purposes and in the treatment of patients
- Nonprofit clinics for scientific, mechanical, and medicinal purposes and in the treatment of patients

Community pharmacies cannot legally obtain or use tax-free alcohol. Hospitals that purchase tax-free alcohol may use it only for medicinal, mechanical, and scientific purposes and in the treatment of patients. Tax-free alcohol may never be used in beverages or food products and medicines made with tax-free alcohol may not be sold to outpatients. Medicines compounded on hospital premises for inpatients may be sold if a separate charge is made. Outpatient charity clinics may furnish medicines made with tax-free alcohol to outpatients if they do not charge. The sale of tax-free alcohol by hospitals to retail pharmacies and physicians' offices is prohibited.

Tax-free alcohol must be stored in a securely locked storeroom with the labels and markings on the containers intact. After the containers are empty, the labels and markings must be obliterated before discarding.

Poison Prevention Packaging Act

Congress enacted the PPPA in 1970 (15 U.S.C. §§ 1471–1474) with the intent of protecting children from accidental poisonings with "household substances." The law defines a "household substance" as any substance that is customarily produced for or used in the household and is designated:

- A hazardous substance in the federal Hazardous Substances Act
- An economic poison under the federal Insecticide, Fungicide and Rodenticide Act
- A food, drug, or cosmetic under the FDCA
- A household fuel when stored in a portable container

The FDA enforced the PPPA until 1973, when this responsibility was placed with the Consumer Product Safety Commission (CPSC). The CPSC has noted that the PPPA has resulted in remarkable declines in the reported deaths of children as the result of accidental ingestion of household substances. However, the CPSC also cautions that among children younger than 5 years of age there is still an average of 30 deaths per year and 78,000 children who are seen in emergency departments following poisonings. (See *Poison Prevention*

Packaging: A Guide for Healthcare Professionals at https://www.cpsc.gov/s3fs-public/384.pdf.)

The act requires the use of child-resistant containers for packaging most OTC drugs and nearly all prescription drugs that the pharmacist will dispense directly to the consumer. These containers must be manufactured such that 80% of the children less than 5 years of age cannot open them, whereas at least 90% of adults can.

A drug may be dispensed only one time in a child-resistant container or vial because continued use compromises the effectiveness of the container. If the container is glass or threaded plastic, however, the CPSC permits reuse of the container as long as it is dispensed with a new safety closure. The commission has indicated that the pharmacist may dispense drugs in reversible containers (those with closures that are child-resistant when used on one side and not child-resistant on the other) as long as they are dispensed in the child-resistant mode. However, the commission continues, this practice is strongly discouraged because it could result in the use of the noncomplying packaging by those able to use the child-resistant packaging without difficulty.

Although pharmacists must normally dispense oral prescription drugs in child-resistant packaging, the law exempts drugs dispensed pursuant to prescription from the packaging requirement if either the physician prescribing the drug or the patient receiving the drug requests noncompliant containers. These requests may be oral, although the pharmacist may be wise to document each request. Preferably, the pharmacist should have the patient sign a statement that the patient requested a noncompliant container. Patients may make a blanket request that all their medications be dispensed in noncompliant packaging; however, prescribers may not, except for refills of the prescription. Blanket requests by patients should be in writing and the pharmacist should periodically check with the patient to ensure that the patient continues to prefer noncompliant packaging. The commission has indicated that it would be legal but not preferable for prescribers simply to check a box on a prescription blank to indicate that the drug be dispensed in a noncompliant package. This practice could encourage excessive use of noncompliant packages.

As another exemption, the PPPA allows manufacturers to market one size of an OTC product for elderly or handicapped individuals in noncompliant packaging. The package must contain the statement, "This Package for Households Without Young Children." If the label is too small for this statement, it may contain the warning, "Package Not Child-Resistant." If the size marketed in noncompliant packaging happens to be a popular size, the manufacturer must also market it in child-resistant packaging.

Drugs dispensed to institutionalized patients are exempt from the act if they are to be administered by the institution's employees.

All legend drugs and controlled substances must be packaged in child-resistant containers, except:

- Sublingual dosage forms of nitroglycerin
- Sublingual and chewable forms of isosorbide dinitrate in strengths of 10 mg or less
- Sodium fluoride products containing not more than 264 mg of sodium fluoride per package
- Anhydrous cholestyramine in powder form
- Methylprednisolone tablets containing not more than 84 mg of the drug per package
- Mebendazole tablets containing not more than 600 mg of the drug per package
- Betamethasone tablets containing not more than 12.6 mg of the drug per package
- Potassium supplements in unit-dose forms, including effervescent tablets, unit-dose vials of liquid potassium, and powdered potassium in unit-dose packets containing not more than 50 mEq per unit dose
- Erythromycin ethylsuccinate granules for oral suspension and oral suspensions in packages containing not more than 8 g of the equivalent of erythromycin
- Colestipol in powder form up to 5 g in a packet
- Erythromycin ethylsuccinate tablets in packages containing no more than 16 g of the drug
- Preparations in aerosol containers intended for inhalation therapy
- Pancrelipase preparations
- Prednisone tablets containing not more than 105 mg per package
- Cyclically administered oral contraceptives, conjugated estrogens, and norethindrone acetate tablets in manufacturer's memory-aid (mnemonic) dispenser packages
- Medroxyprogesterone acetate tablets
- Sucrase preparations in a solution of glycerol and water
- Oral dosage form products containing aspirin and acetaminophen must comply with the act's packaging requirements, except:
    - Effervescent tablets containing aspirin or acetaminophen other than those intended for pediatric use. The dry tablet must contain less than 15% of aspirin or acetaminophen, the tablet must have an oral LD50 in rates of greater than 5 g/kg body weight, and the tablet placed in water must release at least 85 ml

of carbon dioxide per grain in the dry tablet when measured stoichiometrically at standard conditions.
- Unflavored aspirin- or acetaminophen-containing preparations in powder form not intended for pediatric use that are packaged in unit doses providing not more than 15.4 grains of aspirin or 13 grains of acetaminophen per unit dose and that contain no other substances subject to the provisions of the Act.

The PPPA also allows for a procedure to obtain exemptions from child-resistant packaging in the form of a formal petition. Most such petitions come from the manufacturer of the product and are generally for a specific package size of an oral prescription drug.

A few other products covered by the PPPA, subject to specified requirements, include:

- Furniture polish
- Methyl salicylate
- Sodium and potassium hydroxide
- Turpentine
- Kindling and illuminating preparations
- Methyl alcohol
- Sulfuric acid
- Ethylene glycol
- Iron-containing drugs
- Dietary supplements containing iron
- Solvents for paint or other similar surface-coating material

TAKE-AWAY POINTS

- If community pharmacies use alcohol in compounding, it is most likely tax-paid ethyl alcohol.
- Hospitals, hospital pharmacies, and nonprofit outpatient clinics may use tax-free alcohol to compound drug products for their patients, provided certain requirements are followed.
- The CPSC is responsible for enforcing the PPPA, which requires the use of child-resistant containers for packaging most OTC drugs and nearly all prescription drugs that the pharmacist will dispense directly to the consumer.
- A drug may be dispensed only one time in a child-resistant container, unless it is glass or threaded plastic, in which case it may be reused with a new safety closure.
- Either the physician prescribing the drug or the patient may request noncompliant containers for a dispensed prescription drug. These requests may be oral, but writing is preferable.
- The patient may make a blanket request for noncompliant containers orally, but writing is preferable and the pharmacist should recheck the request with the patient periodically.
- Certain drugs are exempt for the PPPA, including sublingual nitroglycerin and sublingual and chewable isosorbide dinitrate in strengths of 10 mg or less.

STUDY SCENARIO AND QUESTIONS

Mr. Thomas is an elderly patient who requests non-child-resistant containers when he can remember. When he cannot remember, the pharmacy dispenses his medications in child-resistant containers. One day, he complained to his physician. When the physician called in a new prescription for Mr. Thomas, he told the pharmacy to dispense all of Mr. Thomas's prescriptions in non-child-resistant containers.

1. Is it permissible for the physician to do this?
2. If not, what should the pharmacy do to prevent Mr. Thomas from receiving child-resistant containers in the future?

Drug Advertising by Pharmacies

In contrast to manufacturers, pharmacists are not usually interested in advertising the merits of drug products, but rather the prices of these products. Price advertising by pharmacists is regulated primarily by state laws and regulatory agencies, but the First Amendment applies no less to pharmacy advertising than it does to manufacturer advertising.

Price Advertising

The FDA considers the advertising of prescription prices by pharmacists to be reminder advertising.

Under 21 C.F.R. § 200.200, prescription drug reminder advertisements, intended to provide price information to consumers, are exempt from the requirements of the advertising regulations (21 C.F.R. § 202.1), provided certain conditions are met:

- The only purpose of the advertising is to provide information on price, not information on the drug's safety, efficacy, or indications for use.
- The advertising contains the proprietary name of the drug, if any; the established name (generic), if any; the drug's strength; the dosage form; and the price charged for a specific quantity of the drug.
- The advertising may include other information such as the availability of professional or other types of services, as long as it is not misleading.
- The price stated in the advertising shall include all charges to the consumer; mailing fees and delivery fees, if any, may be stated separately. Any reminder advertising that is not in compliance with the regulations may be the subject of regulatory action.

Product Advertising: Strict Liability

Occasionally, pharmacists become involved in the advertising of OTC products that is not reminder advertising. In these situations, the Federal Trade Commission Act is most applicable and, in fact, establishes a strict liability standard for those who participate in false advertising. The FTC Act prohibits deceptive or false advertising. In *Porter & Dietsch, Inc. v. Federal Trade Commission*, 605 F.2d 294 (7th Cir. 1979), the FTC brought action not only against the manufacturer of the X-11 tablets but also against the Pay 'n Save drugstore chain. Pay 'n Save's only connection with the X-11 advertising was its participation in Porter & Dietsch's cooperative advertising program, through which it received advertising materials for publication under Pay 'n Save's name. Pay 'n Save had no knowledge that the advertisements were false or unsubstantiated.

Pay 'n Save argued that it should not be held liable for its use of advertisements prepared by others. The court, however, found the drugstore chain liable and cited § 12(a) of the act, which provides, "It shall be unlawful for any person, partnership, or corporation to disseminate, or cause to be disseminated, any false advertisement." Stated the court, "The statute does not make mental state an element of violation and creates no exemption from liability for parties not involved in the creation of the false advertising or for unwitting disseminators of false advertising" (605 F.2d at 309).

The FTC signaled an aggressive position against the deceptive and false marketing of dietary supplements, testifying before a Senate committee in 2009 that marketers of dietary supplements and other products have become very bold in their medical benefit claims, causing health and safety concerns. In 2009, the FTC announced that Rite Aid agreed to pay $500,000 to settle charges for the deceptive advertising of its product, "Germ Defense," for touting the product as able to prevent, treat, or reduce the severity of colds and flu. This settlement came after an FTC action and a consumer class action lawsuit against Airborne Health for the false advertising of its cold prevention products that Airborne agreed to settle for $30 million in 2008. A consumer class action suit against Walgreens for its generic equivalent of Airborne resulted in a settlement in 2009, in which the chain agreed to pay each claimant consumer up to $14.97 or provide a free flu shot. These actions indicate that pharmacies must not only be concerned with a more aggressive FTC, but with class action lawsuits by consumers as well.

State Advertising Laws: The Virginia Case and the First Amendment

Before 1976, many state laws prohibited pharmacists from advertising prescription drug prices. Attempts by chain pharmacies to invalidate these laws as not reasonably related to the public health, safety, and welfare generally failed. (See *Supermarkets General Corporation v. Sills*, 225 A.2d 728 (N.J. Sup. Ct. 1966); *Patterson Drug Co. v. Kingery*, 305 F. Supp. 821 (W.D. Va. 1969); and *Mississippi State Board of Pharmacy v. Steele*, 317 So. 2d 33 (Miss. 1975)). In 1976, however, in the landmark case *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976), the U.S. Supreme Court held that such state statutes violate the First Amendment protection of free speech. In a reversal of previous decisions, the Court found that commercial speech does enjoy limited First Amendment protection.

At issue in *Virginia* was the constitutionality of a Virginia statute that declared the publishing, advertising, or promoting of any amount, fee, premium, discount, or rebate for any prescription drug to be unprofessional conduct. The plaintiffs-appellees in the case were consumers who contended that the law violated the First Amendment of the U.S. Constitution. *Virginia* raised two unique issues to

the Court: (1) Does the First Amendment right of free speech apply to the listeners or recipients of the speech? (2) Does the First Amendment apply to commercial speech?

In answer to the first issue, the Court stated, "If there is a right to advertise, there is a reciprocal right to receive the advertising and it may be asserted by these appellees" (425 U.S. at 757). Regarding the second issue, the Court found that, even if an advertiser's interest is purely economic, the advertiser does not lose First Amendment protection. In fact, continued the Court, the consumer may have as keen an interest in the free flow of commercial information as in the most urgent political debate. The Court was impressed by the consumers' arguments that prescription prices vary greatly from pharmacy to pharmacy and that those most affected by the suppression of prescription drug price information are the poor, the sick, and particularly the aged. These groups tend to spend a disproportionate amount of their income on prescription drugs, yet they are the least able to ascertain by shopping at the various pharmacies where they should spend their scarce dollars. Stated the Court, "It is a matter of public interest that those [consumer] decisions, in the aggregate, be intelligent and well informed. To this end, the free flow of commercial information is indispensable" (425 U.S. at 765).

The Virginia pharmacy board contended that allowing price advertising would drive service-oriented pharmacies out of business; encourage consumers to shop around, thus making medication monitoring impossible; and damage the professional image of the pharmacist. The Court rejected all the state pharmacy board's reasons for the advertising ban and replied that the state appeared to be protecting its citizens by keeping them ignorant. The Court felt that the advertising ban would not achieve the state's objectives:

> There is, of course, an alternative to this highly paternalistic approach. That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them. If they are truly open, nothing prevents the "professional" pharmacist from marketing his own assertedly superior product, and contrasting it with that of the low-cost, high-volume prescription drug retailer. But the choice among these alternative approaches is not ours to make or the Virginia General Assembly's. It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us. Virginia is free to require whatever professional standards it wishes of its pharmacists; it may subsidize them or protect them from competition in other ways. But it may not do so by keeping the public in ignorance of the entirely lawful terms that competing pharmacists are offering (425 U.S. at 770).

The *Virginia* decision not only opened the doors for pharmacists to advertise prescription drug prices, but also ultimately affected other professions as well. For example, in a subsequent Supreme Court decision, *Bates v. State Bar of Arizona*, 443 U.S. 350 (1977), the Court declared state laws that prohibited the advertising of legal services unconstitutional.

Although the Court did not hold in *Virginia* that pharmacists must advertise prescription price information, some states have chosen to mandate that pharmacists provide such information on the request of the consumer. The *Virginia* decision does not prohibit states from regulating the false and misleading advertising of pharmacy goods and services, and nearly all state laws prohibit such advertising. In addition, some states prohibit pharmacists from advertising professional superiority.

The *Virginia* decision does not bar a state from making it illegal for pharmacists to offer discounts or rebates in connection with the sale of drugs. In the matter of *CVS Pharmacy v. Wayne*, 561 A.2d 1160 (N.J. 1989), the CVS pharmacy chain distributed mail circulars advertising a special price of $3.00 for one week for prescription drugs. The state board of pharmacy ruled that the chain was guilty of unprofessional conduct for violating a New Jersey law that prohibited the distribution of discounts, premiums, or rebates, except for trading stamps and to those older than 62 years of age. The pharmacy first brought legal action in federal court, arguing that the New Jersey law unconstitutionally restricted its right of free speech, but the case was dismissed. In state court, CVS argued that the law was unconstitutional on other grounds, especially because it discriminated between those younger and older than 62 years of age. The state court, while acknowledging that the law has several flaws and may not be the best method of achieving the legislative purpose, sustained the validity of the law. The court

established an insurmountable burden of proof for CVS by stating that it would presume that every state statute attempts to protect the public health, safety, and welfare, as long as it attempts to do so in a reasonable manner.

As *Virginia* demonstrates, any government attempt—federal or state—to regulate advertising to protect consumers or protect competition must be weighed against the First Amendment rights of advertisers and consumers.

TAKE-AWAY POINTS

- Price advertising of prescription drug products by pharmacies is considered reminder advertising and is exempt from advertising regulations, provided certain conditions are met.
- The FTC Act establishes a strict liability standard for pharmacies that participate in false or deceptive advertising of OTC products.
- The *Virginia* decision established that the First Amendment applies to commercial speech as well as to the listeners or recipients of the speech. It also established that well-intended, paternalistic laws whose result is depriving consumers of information will be ruled unconstitutional.

STUDY SCENARIOS AND QUESTIONS

1. Blevco Pharmacy and Dietco, the manufacturer of an OTC diet product, entered into a contract whereby in local promotional television ads, Dietco would tout Blevco as the place to purchase the product. In those ads, unknown to Blevco, Dietco engaged in false and misleading advertising. The FTC brought action against both Blevco and Dietco. Explain the liability or lack thereof of each party.
2. A new state law allows pharmacists to prescribe and dispense oral contraceptive drugs from a licensed pharmacy. Clinic Pharmacy placed an ad that it would furnish a one month supply of a particular brand for $25. However, when patients requested the product, the pharmacy added a $5 consultation fee, resulting in the patient cost being $30. Several patients sued Clinic Pharmacy for false advertising. Clinic Pharmacy invoked the First Amendment and the *Virginia* decision in its defense. Explain whether Clinic's defense will prevail.

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CASE STUDIES

Case 3-1 *Pharmaceutical Manufacturers Association v. Food and Drug Administration*, 484 F. Supp. 1179 (D. Del. 1980)

Issue

Whether the FDA has the authority to promulgate a regulation requiring that patient information PPIs be provided to patients for whom estrogen-containing drugs are prescribed.

Overview

Package inserts are labeling directed at healthcare professionals. Historically, the FDCA had left it up to prescribers and dispensers to determine what written drug information should be provided to patients for prescription drugs. This policy changed somewhat in the mid-1970s, however, because the FDA believed that PPIs should be mandated for certain prescription drugs, and enacted regulations to this effect. The regulations angered pharmacy organizations, which were primarily concerned about the logistics, cost, and effort of storing and distributing these PPIs. As you read this case, consider whether PPIs are necessary to protect the health and safety of patients prescribed estrogen drugs. Is it an unjust governmental intrusion for the government to dictate to healthcare providers what information they should tell patients? On what basis does the FDA have the regulatory authority to require patient information? Should PPIs be required for all prescription drugs? Is there a need for uniformity in the written information provided to patients by pharmacists? How does the Medication Guide program differ from the PPI program? Should pharmacy be supportive of or opposed to the Medication Guide program and why?

The court related the facts of the case as follows:

> In this case, plaintiffs, the Pharmaceutical Manufacturers Association, the American College of Obstetricians and Gynecologists, the National Association of Chain Drug Stores, Inc., Private Medical Care Foundation, and others challenge the validity of a regulation promulgated by the Food and Drug Administration which requires certain information to be provided to patients for whom drugs containing estrogens are prescribed.
>
> The agency's action came as a result of several studies published in 1975 that indicated an association between the use of conjugated estrogens and an increased risk of endometrial cancer in women.

The FDA published the rule in July 1977. Before the rule could take effect on September 20, 1977, however, the plaintiffs brought suit seeking a motion for a preliminary injunction. That motion was rejected; they then filed this motion for a summary judgment.

> Plaintiffs and plaintiff-intervenors raise a number of challenges to the regulation. First, they contend that the FDA lacks statutory authority to require patient packaging inserts for prescription drugs. They next assert that such a requirement is an unconstitutional interference with the practice of medicine. Finally, they challenge the adequacy of the FDA's findings and conclusions embodied in the preamble to the regulation and argue that, based on the administrative record, the regulation is "arbitrary, capricious, an abuse of discretion …

The court began its analysis by first noting that the FDA has broad rule-making authority under § 701(a) of the FDCA, and then took account of the relevant statutes.

Section 502 reads in pertinent part:

> A drug or device shall be deemed to be misbranded
>
> (a) If its labeling is false or misleading in any particular.
>
> (f) Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use….
>
> Section 201, 21 U.S.C. § 321, the "Definition" section of the Act, describes the concept of "misleading" in the following terms:
>
> (n) If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article….

Reading the statutes together with the FDA's authority under § 701(a), the court felt there was sufficient support for the regulation on the basis of congressional intent that users of both prescription and nonprescription drugs should receive information material to the consequences of using the drug. The plaintiffs disagreed.

> The plaintiffs acknowledge that Sections 201 and 502 may be read in this manner, but maintain that this reading is contrary to the legislative history of the 1938 Act and is specifically precluded by the enactment of the Durham-Humphrey Amendments to the Act in 1951.
>
> Relying on the legislative history of the 1938 Act, the plaintiffs assert that Section 502(a) was never intended to apply to drugs dispensed on prescription. I find nothing in that legislative history to support this position. Indeed, all the evidence persuades me that the opposite is true. Despite a number of requests from representatives of the medical profession that prescription drugs be exempted from all labeling requirements, the final version of the Act provided an exemption only with respect to certain identified requirements. Section 503(b) exempted any drug dispensed on a written prescription from the labeling requirements of Section 502(b) (relating to quantity of contents) and 502(e) (relating to common names), and exempted prescription narcotics from the requirement that the label carry a warning that the drug may be habit forming, so long as the prescription was not refillable. It did not, however, exempt prescription drugs from the requirements of either 502(a) or 502(f), and both were understood to apply fully to all drug preparations.

The plaintiffs continued by arguing that § 503(b) of the Durham-Humphrey Amendment exempts prescription drugs from the "warnings against misuse" and "adequate directions for use" requirements of § 502 when the drugs are prescribed by physicians and dispensed and labeled pursuant to law. The court found this to be true and that it is the intent of § 503(b) that physicians be the primary source of adequate directions for use and adequate warnings against misuse. However, continued the court, this does not mean that Congress meant to strip the commissioner of regulatory authority.

> Plaintiffs' argument glosses over the fact that while prescription drugs were exempted from the requirements of Section 502(f) in 1951, they were not exempted from the requirement of Section 502(a), that their labels not be misleading.
>
> Thus, while plaintiffs are correct in pointing out that the effect of the Section 503(b)(2) exemption as enacted in 1951 was to make the prescribing physician the primary source of information available to a consumer of a prescription drug, this does not mean that Congress intended to leave this matter to the unregulated discretion of the prescribing physician. The retention of Section 502(a) as a regulatory provision applicable to prescription drugs precludes one from attributing that intention to Congress. The long and short of the matter is that Congress intended patients using prescription drugs, as well as those using over-the-counter drugs, to receive "facts material with respect to consequences which may result from the use of the (drug) … under the conditions of use prescribed in the labeling or under such conditions of use as are customary and usual."

The court, then, addressed the plaintiffs' constitutional challenges. The plaintiffs first advanced that the practice of medicine is within the police powers of the state and not the federal government. The court quickly rejected this argument, however, finding that the federal government also has jurisdiction in this area as a reasonable exercise of the power vested in Congress by the Constitution.

The plaintiffs next argued that mandating PPIs unconstitutionally interferes with the practice of medicine and strips the physician of the right to exercise professional judgment.

> Turning to plaintiff's view of a physician's right to exercise professional judgment, it is important to focus on what the challenged regulation does not do. The regulation at issue here does not forbid a physician from prescribing conjugated estrogen drugs, or limit the physician's exercise of professional judgment in that regard. Nor does it limit the information the physician may impart to his or her patients concerning estrogens. If the physician disagrees with a perceived "slant" of the labeling provided by the manufacturer, or with the facts stated therein, he or she is free to discuss the matter fully with the patient, noting his own disagreement and views. The sample labeling encourages the patient to have this kind of open discussion with her doctor.
>
> When these limitations on the effect of the challenged regulation are considered, it becomes apparent that the plaintiffs urge recognition not of a right to exercise judgment in prescribing treatment, but rather of a right to control patient access to information. As I pointed out in my earlier Opinion, labeling is only one of many sources from which patients receive information about drugs, and the control which the plaintiffs claim to have possessed prior to the challenged regulation is largely illusory. But there is a more fundamental problem with their position. There simply is no constitutional basis for recognition of a right on the part of physicians to control patient access to information concerning the possible side effects of prescription drugs.
>
> By holding that physicians do not possess the constitutional right which plaintiffs claim, I do not overlook the affidavits of numerous experienced physicians who foresee patient anxiety and ruptured physician-patient relationships as a result of the implementation of the regulation. These matters are clearly relevant to an evaluation of the wisdom of the regulation. They do not, however, render it constitutionally infirm.

Dispensing with the constitutional issue, the court lastly turned its attention to the issue of whether the FDA provided a basis and purpose for the regulation as required by administrative law. The plaintiffs felt the regulation was promulgated arbitrarily and capriciously (an abuse of administrative discretion) because the regulation did not provide an exception for those situations in which the physician might want to withhold the information from the patient. The court replied that whether the regulation is arbitrary and capricious depends on whether the regulation was "based on a consideration of the relevant factors and whether there has been a clear error of judgment." The court then found that the agency had given considerable attention to whether to include the option.

> Given the purposes of the Act and its mislabeling provisions, the touchstone of any decision of the Commissioner is the safety and health of the patient. With this touchstone in mind, the primary factors to be weighed in deciding to grant or deny the option for which plaintiffs press are (1) the extent and character of the risk involved in using estrogen drugs, (2) the efficacy of, or the benefit to be derived from, providing patients with information concerning that risk, and (3) the extent and character of any risk involved in exposing all patients to that information. The Commissioner explains his views in each of these areas. First, it is apparent that he considers the risk associated with the use of estrogen drugs to be great, in terms of both the number of users and the gravity of the consequences to those who are adversely affected. Second, he explains that he finds this to be an area where patients are capable of understanding the advantages and risk of use and where most patients because of the nature of the condition for which the drug is prescribed, have a real option to use or not to use it. And, finally, on the other side of the balance, the Commissioner states that, unlike the situation with respect to some other drugs, he finds no likelihood of a substantial adverse effect on patients from exposure to the information provided by the labeling.
>
> If a patient decides to follow the instruction of her physician, the Commissioner does not believe that patient labeling will significantly increase the incidence of suggestion-induced side effects. Suggestion effects, moreover, seem to play a minimal role in determining serious adverse reactions. It is, in any event, possible to hypothesize beneficial as well as negative effects of suggestion. Clear expectations about the effects of drug therapy, reinforced by patient labeling, may make patients more sensitive and aware of certain physical or psychological reactions. Effects which might otherwise go unnoticed may be identified as drug related. Although this may have the effect of nominally increasing the reported incidence of less serious adverse reaction, it also may have beneficial results. Patients may be more sensitive to "warning signals" of serious adverse effect…. It is the Commissioner's opinion that the possible positive effects of supplying accurate side-effect information outweigh the possible negative effects.
>
> While reasonable minds might reach different conclusions, this explanation of the Commissioner's reasoning is sufficient to demonstrate that the challenged regulation is the product of a rational process.

The court granted the FDA's motion for summary judgment, finding that the FDA does have statutory authority to require patient labeling; that the regulation does not interfere with any constitutionally protected rights of physicians; and that the agency's reasoning is sufficiently articulated and supported.

Notes on Pharmaceutical Manufacturers Association v. Food and Drug Administration

1. The plaintiffs attempted to distort the intent of the Durham-Humphrey Amendment, which in part exempts prescription drugs from § 502. If not for the amendment, pharmacists would have to label every drug dispensed in conformance with all the requirements of § 502. Not a practical proposition! The amendment recognizes that prescription drugs cannot be labeled with adequate directions for use, thus requiring the guidance of healthcare professionals. Its intent is not to provide healthcare professionals with total discretion to control patient information. The plaintiffs also adopted an extremely paternalistic position by arguing that only they are qualified to determine what information should be provided to patients. In fact, taking this position and denying the government's right to require patient information is contrary to the ethical and legal principle that patients have a right to be informed. Moreover, the fact that the physicians asserted they have a constitutional right to practice medicine without government interference of their professional judgment completely overstates their role. If anything, it is the patient who may really have a constitutional right to receive drug information.
2. The FDA had proposed in the 1970s to make PPIs mandatory for several drugs, but because of tremendous opposition, dropped this plan. The agency made no further directives regarding patient information until the Medication Guide program was proposed. Somewhat surprisingly, the MedGuide program also faced vigorous opposition by healthcare professionals, even in the present climate in which patients are demanding drug information. The agency's interest in the MedGuide program also was somewhat surprising considering the passage of OBRA '90 and the offer to counsel requirement. However, OBRA '90 does not mandate that patients receive written information about their drugs, and the agency was obviously dissatisfied with the information healthcare providers were providing patients. One problem with the written information distributed by pharmacies is a lack of standardization, a problem the FDA would like to rectify.
3. Many pharmacies now routinely provide patients with some type of written information. In fact, one can make a strong case that providing written information constitutes the legal standard of care. In a lawsuit by a patient alleging that the pharmacist had a legal duty to warn of the adverse effect suffered by the patient, providing written information that contains the warning would mitigate the probability of the pharmacist being found negligent.

Case 3-2 *Ramon v. Farr*, 770 P.2d 131 (Utah 1989)

Issue

Whether the package insert constitutes prima facie evidence of the standard of care.

Overview

It is not uncommon for healthcare practitioners to prescribe and dispense medications for off-label uses or dosages. As discussed earlier, it is not a violation of federal or state law to do so. However, deviating from a drug's labeling can present civil liability concerns in the event of a bad outcome. As you read this case, consider why it is that many drugs have off-label uses. What role does the product's labeling play in determining liability? Should patients be informed that the drug is being prescribed for an off-label use? Does the healthcare provider face a greater risk of liability when deviating from the labeling? If so, how can that risk of liability be minimized?

The court first described the facts of the case, which can be summarized as: Dr. Boyd Farr, who was the attending physician for Alicia Ramon during the delivery of her baby, performed a cervical block by injecting Ramon in the cervical region with Marcaine approximately 1 hour before the birth.

> At birth, Jaime appeared to be a normal, healthy child, but he began to show symptoms of serious problems several hours later. He was transferred to an intensive care unit and later suffered grand mal seizures. The parties agree that Jaime has serious permanent physical and mental defects and can never be expected to reach normal ranges of mental or physical development.

Ramon and her husband sued the hospital and Dr. Farr on behalf of their son, and the hospital settled out of court. The trial court, finding for Dr. Farr, refused to give the jury the instructions requested by the Ramons that would have made the manufacturer's package insert prima facie evidence of the applicable standard of care. The Ramons appealed, claiming that the trial court erred in refusing to give the jury the instructions.

> The Ramon' first claim arises from the trial court's refusal to submit their second theory to the jury. That theory apparently was that the mere injection of the mother and not the child with Marcaine was negligent and caused Jaime's condition. The trial court refused to give a proposed jury instruction pertinent to that theory. The instruction stated that the use of Marcaine for a paracervical block when that use was not recommended by the manufacturer is prima facie evidence of negligence. Both the package insert that was shipped with the Marcaine and the 1980 (34th ed.) *Physicians' Desk Reference* ("PDR") at page 695 read: "Until further clinical experience is gained, paracervical block with Marcaine is not recommended." The Ramons claim that the trial court erred in rejecting the proposed instruction.

The appellate court found that the trial court was justified in its determination because the Ramons failed to present sufficient evidence that the Marcaine caused the injury. The court went on to note:

> But even if there were sufficient evidence of causation to submit the Ramons' second theory to the jury, we have another reason for upholding the trial court's refusal to give the proposed instruction: we decline to adopt the legal rule that it states. The Ramons observe that the Utah courts have not settled the question of the legal effect to be given recommendations that are issued by drug manufacturers in the form of package inserts and PDR entries. They argue that we should follow the rule that the insert constitutes prima facie evidence of the applicable standard of care. In other words, they ask us to hold that the mere introduction in evidence of an insert or PDR entry shifts the burden of proof on the standard of care to the defendant physician.
>
> In response, Dr. Farr first observes that the insert language at issue did not contraindicate the use of Marcaine for paracervical blocks, but simply stated that the manufacturer was not recommending the use of the drug without further testing. He urges us to hold that the package insert is only some evidence that the jury can take into account in determining the standard of care and that the plaintiff in a medical malpractice action usually bears the burden of introducing evidence on the standard of care in the form of expert testimony. In support of this position, Dr. Farr argues that the decision to use a particular drug is always a matter of judgment for the physician based on all information available, including medical journals, advice from colleagues, professional experience, and the information provided by manufacturers. He contends that it would be unrealistic to straitjacket a physician's treatment choices with package inserts.

The court continued by recognizing that decisions differ on whether the package insert should be prima facie evidence of the standard of care.

> One line of authority relied on by the Ramons is represented by *Mulder v. Parke Davis & Co.*, 288 Minn. 332, 181 N.W.2d 882 (1970). In *Mulder*, the Minnesota Supreme Court held that when a drug manufacturer provides recommendations concerning the administration and proper dosage of a prescription drug and also warns of the dangers inherent in its use, a physician's "deviation from such recommendations is prima facie evidence of negligence if there is competent medical testimony that his patient's injury or death resulted from the doctor's failure to adhere to the recommendations." *Mulder* has been followed by the courts of only a few other states. And the Minnesota courts have since retreated somewhat from the *Mulder* standard. Minnesota presently requires a *Mulder* prima facie negligence instruction only when the manufacturer's instructions contain a clear and explicit warning against the type of use that is alleged and a deviation from that recommendation caused the injury. In the present case,

the manufacturer did not make such a clear and explicit recommendation against the use of Marcaine for a paracervical block. Rather, it simply did not recommend its use until further studies were performed. Thus, even under the current Minnesota rule, the Ramons would not be entitled to their proposed jury instruction.

In any event, we decline to follow the *Mulder* rule, either as originally articulated or in its current incarnation. Rather, we think the better rule is that manufacturers' inserts and parallel PDR entries do not by themselves set the standard of care, even as a prima facie matter. A manufacturer's recommendations are, however, some evidence that the finder of fact may consider along with expert testimony on the standard of care.

The court noted that this is the favored approach of most other jurisdictions as well.

Although package inserts may provide useful information, they are not designed to establish a standard of medical practice, and their conflicting purposes make it extremely unlikely that they could be so designed. We therefore conclude that the trial court acted properly in refusing to give the Ramons' requested jury instruction on the effect of the insert. The judgment was affirmed.

Notes on Ramon v. Farr

1. Manufacturers often submit a drug for FDA approval with a minimum number of indications in order to get the product marketed as quickly as possible. Subsequently, they will obtain approval for additional indications. Moreover, for liability reasons, manufacturers actually may tend to overwarn in some instances. Therefore, prescribers often prescribe drugs for off-label uses or dosages or, contrary to warnings in the labeling, when their professional judgment warrants.
2. *Ramon* represents how most courts would determine the role of the package insert in determining a legal standard of care. In *Morlino v. Medical Center of Ocean County*, 152 NJ 563, 706 A.2d 721 (1998), a physician prescribed ciprofloxacin for an infection in a pregnant woman even though the package insert warned against the use in pregnant women. The plaintiff alleged that the ciprofloxacin caused the death of her fetus. The physician knew the risk but determined that the benefit of prescribing ciprofloxacin outweighed the risk in this case. Finding for the physician, the court ruled that the package insert can be admitted into evidence to show the standard of care as long as expert testimony is presented to explain the standard to the jury.
3. The real issue for a pharmacist confronted with a prescription for a drug prescribed for an unlabeled use or dosage is to exercise professional judgment. This means researching the issue to determine if there is a risk of harm to the patient and just how likely and how great that harm might be. The next step is to contact the prescriber to determine first whether the prescriber intended the drug to be used in the manner prescribed and, second, to apprise the prescriber of the risks as determined from the research. If the risk to the patient is likely and/or potentially of great magnitude, the pharmacist should ask the prescriber to justify his or her decision to use the drug in the manner prescribed (e.g., by reference to referred articles in scientific journals). If the use cannot be justified or if the risk to the patient appears too great, the pharmacist may decide to not dispense the drug. If, on the other hand, after researching the issue and discussing the issue with the prescriber, the benefit appears to outweigh the risk, the pharmacist then should dispense the drug but only after counseling the patient about the benefits and risks. At this point, the patient might decide not to take the drug. Finally, the pharmacist must document his or her intervention.

Case 3-3 *Pfizer, Inc. v. Shalala*, 1 F. Supp. 2d 38 (D.C. 1998)

Issue

Is a generic drug with a different sustained release system from the parent drug a generic equivalent to the parent drug?

Overview

The PTRA facilitated the marketing of generic drugs by allowing generic drug sponsors to file ANDAs rather than NDAs. This case provides additional insight into the procedures followed by the FDA to determine if a product is similar enough to the parent drug such that the sponsor may file an ANDA. The plaintiff, Pfizer, contends that the products are not similar enough and, of course, has the ulterior motive of restraining competition. At issue in this case is whether two drug products can be considered generically equivalent if the manner in which they release the active ingredient is substantially different. This is a controversial issue with drug manufacturers because dosage form technology has advanced tremendously in the past few years. As you read this case, ask yourself: Is the FDA's position correct? The FDA is essentially saying that the means in which the generic product releases the active ingredient

in the body is irrelevant, as long as the generic drug product establishes bioequivalence to the parent drug. In other words, the end is more important than the means. Is there a public health problem with this interpretation? Also, consider what the effect on generic competition would be if Pfizer's position is correct. Would companies just continually redesign the dosage forms of their products to subvert competition? Finally, if Pfizer's position is rejected, what effect will this have on the science of dosage form design? Will companies have any market incentive to expend money on innovative dosage form technology if competitor products without the technology are deemed generically equivalent?

The court first provided the facts of the case:

The FDA accepted an ANDA from Mylan Pharmaceuticals for a generic version of a sustained-release nifedipine tablet. Pfizer is the company that first developed the nongeneric or pioneer version of this drug. Plaintiff Pfizer, Inc., brought this summary judgment action to convince the court to order the FDA to reject Mylan's ANDA on the basis that Mylan's drug does not have the same type of extended-release system as its drug and thus is not an identical dosage form.

> Pfizer's pioneer drug, Procardia XL, is a controlled release drug in which the full dose of the active ingredient in the drug, nifedipine, is released slowly, over time. There are several mechanisms used in controlled release oral drugs in order to regulate the release of a drug's active ingredients. Procardia XL uses a patented oral osmotic pump release mechanism to release the nifedipine it contains. Osmotic release systems function by slowly releasing the drug's active ingredients from a shell; a pump or push component inside the shell swells when gastrointestinal fluid enters the shell to expel the active ingredient. Procardia XL's osmotic pump device is covered by four patents, and the size of the nifedipine crystals used in the drug is also patented. (Unlike Procardia XL, Mylan's nifedipine product is a "conventionally-pressed" tablet that uses an extended-release system other than an osmotic pump to release its active ingredients.)

The court then proceeded to examine the relevant statutes and regulations applicable to the NDA process, noting that Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 to provide for an expedited review process (the ANDA). The court noted that under the FDCA and FDA regulations, the ANDA procedure is available only after the FDA makes a "threshold determination that the ANDA is sufficiently complete to permit a substantive review." Substantive review will occur only if, on its face, the ANDA indicates that the generic drug's active ingredients, route of administration, dosage form, and strength are the same as the pioneer drug. If a generic drug is similar but not identical to the pioneer drug on those factors, the applicant must first file a "suitability petition" to allow the FDA to assess the differences. If approved, the applicant may then file an ANDA.

> If the FDA accepts an ANDA as being properly filed, either because it is sufficiently complete on its face or because a suitability petition has been approved, the FDA then proceeds to the substantive review stage. During the substantive review stage, the FDA goes beyond its preliminary threshold determination and this time thoroughly reviews the sufficiency of the ANDA's information. The applicant must show, inter alia, that the generic product (1) has the same active ingredients, route of administration, dosage form and strength as the pioneer drug, (2) is bioequivalent to the pioneer drug, and (3) is safe under the conditions prescribed, or, in the case of an ANDA that has been filed subsequent to the approval of a suitability petition, the ANDA must contain sufficient information about the particular aspect of the drug that is different from the pioneer drug.
>
> If the FDA finds that the information in the ANDA is sufficient under the FDCA and FDA regulations, it will approve the ANDA and issue a notice that the generic imitation is therapeutically equivalent to the reference listed drug.
>
> If the FDA decides at any point that a proposed generic product varies from the pioneer drug in any of the four statutory categories (active ingredients, rate of administration, dosage form, or strength), it must conclude that the generic drug is only a "pharmaceutical alternative," not a "pharmaceutical equivalent" (21 C.F.R. § 320.1(c) and (d)). This is a great disadvantage to a generic product manufacturer because many state laws require a generic product to be pharmaceutically equivalent to the pioneer drug before it may be substituted for the pioneer drug. It is important to note that any drug manufacturer that seeks approval of a suitability petition before filing an ANDA is relinquishing the "pharmaceutical equivalence" label for its proposed generic product. Generic drugs that are approved through the suitability petition process can only meet the definition of a "pharmaceutical alternative" because the very filing of a suitability petition is an admission that the drug's active ingredients, route of administration, dosage form, or strength is different from that of the pioneer drug.

After reviewing the regulatory framework, the court then focused on the issue of whether the FDA acted properly in accepting Mylan's ANDA on the basis that the generic drug had the same dosage form as Procardia XL. Pfizer contended that the dosage forms of the drugs cannot be the same because they have different release systems. The FDA, however, argued that for the purpose of accepting an ANDA application, the fact that each drug is an extended-release tablet makes them have the same dosage form. Stated the FDA:

> The 74 dosage form descriptions, including the descriptions "extended-release tablet" and "extended-release capsule," that are currently listed in the Orange Book have effectively served the public, the Agency, and the industry. The categories are useful in that they are sufficiently differentiated to make a reasonable distinction based on dosage form, which includes the appearance of the drug.

> However, the categories are also useful in that they are not so narrow as to be virtually product-specific. As a result, these categories have allowed the FDA to make threshold determinations that products have the same dosage form while encouraging manufacturers to develop innovative release technologies and allowing the public the benefit of safe and effective generic drug products.

The court agreed that the FDA's view is reasonable and not inconsistent with the FDCA. The court stated that when a statute fails to define a relevant term such as dosage form, its role is to determine whether the FDA's definition is a permissible construction and is rational and consistent with the statute. Taking issue with Pfizer's contention that the FDA's decision that extended-release dosage forms can be properly categorized on the basis of appearance and route of administration rather than on the basis of the drug's release or delivery mechanism is irrational and outmoded, the court remarked:

> The FDA has offered a more than rational explanation for interpreting "dosage form" the way it has for so many years and for maintaining its current dosage form classification system. Although neither the Congress in the FDCA nor the FDA itself in its regulations has specifically defined the term "dosage form," the manner in which the FDA defines dosage form and applies its definition is rational. It is governed primarily by a list of 74 dosage forms set forth in Appendix C of the FDA's Approved Drug Product with Therapeutic Equivalence Evaluation, 17th ed., commonly known as the "Orange Book." The FDA admits that while this list is not binding on it or on the pharmaceutical industry, it does serve as informal guidance to a generic company on what is considered to be the "same" or "identical" dosage form.
>
> Under the current system, if two drugs fall into the same dosage form in the Orange Book, such as "extended-release tablet," the FDA makes a threshold determination that their dosage forms are the "same" and, all other information being sufficient, it will then accept a generic drug company's ANDA as being filed. In this case, the FDA has preliminarily decided that Mylan's ANDA contained enough information to enable the FDA to make a threshold determination that the dosage form of Mylan's drug (among other things) is the "same" dosage form as Procardia XL, an extended-release tablet.
>
> Under the current FDA regime, an ANDA sponsor therefore may submit an ANDA for a generic drug that has the same active ingredients, route of administration, strength, and dosage form as the pioneer drug but a different formulation and, thus, a different release mechanism as the pioneer drug. In fact, under FDA regulations, the definition of "pharmaceutical equivalents" is "drug products that contain identical amounts of the identical active drug ingredient … in identical dosage forms, but not necessarily containing the same inactive ingredients." This makes sense. If, for instance, a generic tablet that does not use the osmotic pump can perform the same extended release functions as Procardia XL, and can perform them safely, then it is logical that the generic drug would be approved as a generic equivalent of Procardia XL. What else would a generic drug be?
>
> Despite plaintiff's claims to the contrary, there is nothing in the Federal Food, Drug, and Cosmetic Act to indicate that Congress intended the FDA to develop a dosage form classification system based on a drug's release mechanism. When Congress passed the Waxman-Hatch Amendments, the FDA already had an abbreviated drug application procedure in place that utilized a dosage form classification system that was not based on release mechanism differences. Congress' choice not to address or revisit the ongoing FDA system of classifying dosage forms strongly suggests both that it was aware of the system and that it did not intend to change it. Indeed, in light of the principal objectives of the Waxman-Hatch Amendments, this Court sees no reason why Congress would want to change the FDA's interpretation of dosage form or the application of that interpretation.

The court denied Pfizer's claim and awarded summary judgment for the FDA.

Notes on Pfizer, Inc. v. Shalala

1. To support his decision, the judge concluded that the purpose of the Waxman-Hatch Amendments to make more low-cost generic drugs available would be defeated if Pfizer prevailed. He called Pfizer's interpretation of the law "transparently self-serving," in that such an interpretation would suppress generic competition for years.
2. It is important to realize that this decision does not hold that Mylan's product has the same dosage form as Pfizer's. Rather, the court has ruled that the FDA's interpretation of the drug dosage form classification system is reasonable and permissible. In fact, at the time of this trial, the FDA had only accepted Mylan's ANDA for filing and had not considered the merits of the ANDA yet. It is conceivable that the FDA, in the process of reviewing the ANDA, could yet find that the two products are indeed not identical dosage forms. The court recognized this and refused to allow Pfizer to challenge the FDA's acceptance of the ANDA on the basis of ripeness. In other words, courts will not permit judicial review before an agency makes a final determination and until the plaintiff has exhausted all remedies within the administrative agency. If Pfizer had prevailed in this case, Mylan would have been forced to submit a suitability petition, which would have precluded their product from ever being approved as a pharmaceutical equivalent.
3. It is important financially to innovator drug manufacturers that generic drug competitors not be "A" rated to their product. In this situation, the manufacturer can actively market to healthcare providers that their product should not be substituted. In addition, many state laws prohibit the interchange of drugs that are not bioequivalent without specific authorization from the prescriber.

Case 3-4 *Winn Dixie of Montgomery, Inc. v. Colburn*, 709 So. 2d 1222 (Ala. 1998)

Issue

Whether the damage award to a plaintiff injured as a result of a pharmacist substituting a drug that was not generically equivalent to the drug prescribed was appropriate.

Overview

Even though this case is not an FDCA case and is really about damages, it highlights important issues under the FDCA, including substitution without authorization and the issue of generic and therapeutic substitution. In this case, the pharmacist substituted what he thought was a generic equivalent to the drug prescribed, even though the prescriber refused to authorize substitution. The substituted drug was not a generic equivalent and the patient sustained harm. This case not only demonstrates the importance of making certain that the products are generic equivalents, but it also raises the broader issue of when might substitution present a greater risk of harm to the patient, and thus a greater risk of liability for the pharmacist. As you read this case, consider these issues: Does your state allow substitution without prescriber authorization? Can a pharmacist substitute if a patient requests but the physician refuses authorization? Should a pharmacist be able to rely on software? Are there any types of drugs in which generic substitution might cause harm to a patient and thus increase legal risk? What is the difference between generic substitution and therapeutic substitution? Does therapeutic substitution present a greater risk?

The court stated the facts of the case as:

> Mary Catherine Colburn sued Winn Dixie of Montgomery, Inc., and Robert Hagan, alleging that they were negligent or wanton in filling a prescription for her. Specifically, Colburn claimed that Robert Hagan, the pharmacist at a store operated by Winn Dixie of Montgomery, wantonly or negligently dispensed Fiorinal No. 3 as a substitute medication for a prescription of Sedapap. The jury returned a general verdict for Colburn and against Winn Dixie and Hagan, awarding damages of $130,000. The trial court entered a judgment on that verdict.
>
> Winn Dixie and Hagan claim that the judgment should be reversed because the evidence was insufficient to support the damages award. They also argue that the judgment is excessive.
>
> Viewed in the light most favorable to Colburn, the evidence suggests the following: Colburn consulted Dr. Mildred Howell, complaining of migraine headaches. Dr. Howell, knowing that Colburn was allergic to codeine, prescribed Sedapap, which does not contain codeine, to treat Colburn's migraine headaches. Dr. Howell signed the prescription form over a line that stated "product selection permitted"; that statement means that a generic equivalent could be substituted for the name-brand product. Colburn took her prescription to a pharmacy at a Winn Dixie supermarket to have it filled. The Winn Dixie pharmacy did not have Sedapap in stock. Hagan testified at trial that he looked up Sedapap on the Winn Dixie computer drug profile, and that it reported that Sedapap and Fiorinal No. 3 were identical. However, Fiorinal No. 3, which was substituted for Sedapap, is not a generic equivalent to Sedapap; in fact, it contains codeine, the very thing to which Colburn was allergic. In his prescription-error report, Hagan wrote that he had substituted the Fiorinal No. 3 because it was the "closest formula" to Sedapap and he felt certain that the physician would allow the substitution. In addition, at trial Colburn presented evidence indicating that Hagan telephoned Dr. Howell to ask if he could substitute Fiorinal No. 3 for Sedapap, and that Dr. Howell had her assistant tell him that it could not be substituted.

After taking the medication, Colburn went into anaphylactic shock and was rushed to the hospital emergency department, nearly dying on the way. After treatment, she returned home that night but continued to feel side effects, including a severe headache that lasted several days. She presented evidence indicating that but for her husband's swift reaction, she likely would have died of anaphylactic shock. She testified that she is still afraid to take prescription drugs.

> Winn Dixie and Hagan contend that because Colburn suffered no permanent physical injury the $130,000 award is out of proportion to her injury. Winn Dixie and Hagan do not address the propriety of the jury's finding of liability. They simply argue that the amount of the award bears no reasonable relationship to the harm suffered by the plaintiff. However, Winn Dixie and Hagan consented to the jury's use of a general verdict form that did not delineate separate amounts of compensatory damages and punitive damages. Therefore, this Court has no way to determine what portion of the award was intended as punitive damages. In fact, the jury may have intended the entire amount to be compensatory damages.

In fairness to Winn Dixie and Hagan, however, the court decided to consider that part of the $130,000 was punitive in nature and then proceeded to apply the three "guideposts" articulated by the U.S. Supreme Court in *BMW of North America, Inc. v. Gore*, 517 U.S. 559 (1966), to determine whether the punitive award was excessive.

> The first "guidepost" is the reprehensibility of the defendant's conduct. In BMW, the Supreme Court indicated that "indifference to or reckless disregard for the health and safety of others" is an aggravating factor associated with particularly reprehensible conduct. Clearly, this aggravating factor was present in this case. There was evidence that Hagan telephoned Colburn's physician to ask if he could substitute Fiorinal No. 3 for Sedapap and that the physician had her assistant tell him that it could not be substituted. Thus, the jury could have found that the pharmacist received specific instructions from the physician not

to substitute the medication but did so anyway; thus, the jury could have found that Hagan acted with a reckless disregard for Colburn's safety. Further, the Winn Dixie computer drug profile erroneously reported that Sedapap and Fiorinal No. 3 were identical; and the evidence indicates that, even once the error was discovered, Winn Dixie did not correct the information in the computer, thereby increasing the risk of further harm to its customers. This evidence supports a finding of reprehensibility on the part of Hagan and Winn Dixie that would warrant a large punitive damages award.

The second BMW guidepost for determining whether an award of punitive damages is excessive is the ratio of punitive damages to the actual harm inflicted upon the plaintiff. Because the jury awarded general damages, we cannot determine with certainty the ratio of punitive damages to compensatory damages. It is important to note that we do not consider that any compensatory award was based solely on economic loss; rather, we consider it to be based largely upon the obvious mental and emotional distress that Colburn endured because of her life-threatening experience. We conclude that it was well within the right of the jury to award Colburn $130,000 because she experienced the natural terror associated with what she believed to be imminent death.

Finally, the last guidepost BMW gives for determining whether a punitive damages award was excessive is a comparison of the punitive award to the civil or criminal penalties that could be imposed for similar misconduct. In this present case, the maximum penalty under Alabama law for dispensing a different drug or different brand drug in lieu of that ordered or prescribed, without the express permission of the person ordering or prescribing the drug, is a $1,000 fine (Ala. Code 1975, 34-23-8). We must point out that the dispensing of prescription drugs is a matter of public trust and that one who dispenses them carelessly endangers the health and safety of the consumer. A $1,000 fine is a meager sanction for such a serious offense and provides little basis for determining a meaningful punitive damages award.

We affirm that portion of the judgment imposing liability. However, we remand this case for the trial court to make written findings on the issue of excessiveness of the punitive damages award, if, indeed, it determines that any of the award was punitive in nature.

Notes on Winn Dixie of Montgomery, Inc. v. Colburn

1. Although the drug substitution laws do vary from state to state, certain aspects do not. Pharmacists may not legally substitute when prescribers specifically prohibit substitution, and pharmacists may not legally substitute unless the drugs are generically equivalent. The pharmacist did not make a generic substitution but a therapeutic substitution. The products are in the same therapeutic class but are not generically equivalent. For the most part, therapeutic substitution by a pharmacist without specific authorization from the prescriber is illegal. The pharmacist in this case intentionally violated the law, permitting a jury to conclude that the pharmacist's behavior was more than just negligent, but reprehensible, leading to punitive or punishment damages. Pharmacists who violate laws, even unintentionally, run a significantly greater risk of being found liable in a negligence case. Pharmacists who violate laws intentionally risk punitive damages as well.
2. The pharmacist relied on software in this case, but it is unlikely that a court would ever find that a pharmacist can forgo professional judgment on the basis of relying on software. Software is only a tool to help pharmacists, not a replacement for judgment.
3. In most cases, generic substitution would not present any patient risk. Some generics, however, might present patient risk such as drugs with B ratings in the Orange Book and pre-1938 drugs where there is not sufficient evidence of bioequivalence. Some contend that even narrow therapeutic index drugs with A ratings are risky to substitute. Pharmacists should not switch patients stabilized on one generically equivalent drug with another unless the products are bioequivalent. If a substitution among nonbioequivalent drug products is necessary, the prescriber should be contacted to authorize the substitution (this would be the law in many states) and the patient must be counseled.

Case 3-5 *Kennedy v. Kentucky Board of Pharmacy*, 799 S.W. 2d 58 (Ky. App. 1990)

Issue

Whether a pharmacist who resells drugs from the hospital pharmacy inventory to a wholesaler is a wholesaler and whether by doing so has engaged in unprofessional conduct.

Overview

In this case, a hospital pharmacist regularly resold his excess inventory to a drug wholesaler. Although the PDMA was not an issue in this case, perhaps it should have been. The PDMA was passed in 1987 in part to prevent hospitals from reselling prescription drugs that they purchased at preferred prices. Some organizations and individuals made

considerable profits engaging in this secondary market and, in the process, jeopardized public health and safety by selling adulterated and misbranded drugs. As you read this case, consider whether this is the type of situation the PDMA meant to prohibit. Does it matter under the PDMA whether the pharmacist or the pharmacy profited or not from the resales? What might the outcome have been under the PDMA? Consider the two charges made by the board of pharmacy against the pharmacist. What evidence would the board have to bring to win on those two charges—or could the board win?

The court narrated the facts of this case as follows:

> John Kennedy appealed from the judgment of the Clay Circuit Court which affirmed the decision of the appellee, Kentucky Board of Pharmacy, to suspend his license for 1 year and which imposed a $4,000 fine. The board found that Kennedy, a licensed pharmacist, violated KRS 315.036(1) and 315.036(2), and engaged in unethical conduct as contemplated by KRS 315.121(1)(f). We agree with Kennedy that the board erred as a matter of law, necessitating reversal of its findings and conclusions.
>
> The facts are well known to the parties and need not be set out at length in this opinion. Briefly, Kennedy has been a licensed pharmacist for many years and had a permit from the board to operate the Red Bird Hospital Pharmacy. Four times a year Kennedy gathered up his excess drugs [and sold them to a drug wholesaler, Elite Supply Company]. Included in these sales were birth control pills, the invoices for which were stamped by the manufacturer, Wyeth Laboratories, "For clinic use only. This specifically priced merchandise is not intended for resale or distribution outside the clinic."

The court then noted the relevant statutes that included KRS 315.010(6), (7), (10), and (12):

> (6) "Manufacturer" means any person, except a pharmacist, within the Commonwealth engaged in the commercial production, preparation, propagation, compounding, conversion, or processing of a drug, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical synthesis, or both, and includes any packaging or repackaging of a drug or the labeling or relabeling of its container.
>
> (7) "Pharmacist" means a natural person licensed by this state to engage in the practice of the profession of pharmacy.
>
> (10) "Practice of pharmacy" means a health service which includes the dispensing, storage, and instruction as to the proper use of drugs, including radioactive substances, and related devices, the maintenance and management of health and the encouragement of safety and efficacy in those activities.
>
> (12) "Wholesaler" means any person, except a pharmacist, within the Commonwealth who legally buys drugs for resale and distribution to persons other than patients or consumers.

The two statutory provisions that Kennedy was found to have violated were 315.036(1) and (2), which require that manufacturers and wholesalers register with the board, obtain a permit, and pay a fee, and maintain adequate records of all drugs manufactured, received, and sold.

The court then proceeded with its analysis of the case.

> Kennedy's argument, with which we agree, is that the board erred in disciplining him under the statutes pertaining to manufacturers and wholesalers as, by definition, he is neither a manufacturer nor wholesaler. In clear, plain terms the definitions previously set forth specifically exclude a pharmacist from the category consisting of manufacturers and wholesalers. The board argues, and the circuit court agreed, that Kennedy is not entitled to be excluded from the category of a manufacturer or wholesaler when acting as a pharmacist as defined in KRS 315.010(10). We are not persuaded the argument supports the board's decision for two reasons. First, it seems quite reasonable to us that selling excess drugs before they become stale or expire is conduct that would fall within the definition of the "practice of pharmacy." At least there was no evidence to the contrary. Secondly, there are other statutory provisions in the chapter applicable to pharmacists, specifically KRS 315.035 and KRS 315.121, which permit the board to set standards of conduct and to regulate the practice of pharmacy. If Kennedy's conduct in selling excess prescription drugs offended any statute or regulation pertaining to pharmacists, the board has yet to so allege.
>
> It is basic that in construing a statute the courts must examine and give effect to each word, clause or sentence that allows for reasonableness. We must assume the legislature had a purpose for differentiating between "pharmacists" and "wholesalers." To ignore the difference, as did the board, does violence to the well-established principle that words specifically defined by statute "must be given the meaning prescribed by the legislature in construing the statute." Thus we conclude the board erred as a matter of law in disciplining Kennedy for his failure to get a wholesaler's license.
>
> We also agree with Kennedy that the board erred in concluding that his conduct was "unethical or unprofessional" and of a "character likely to deceive, defraud or harm the public." This charge was predicated on the resale of the birth control pills originally obtained from Wyeth Laboratories under invoices indicating the medication was not intended for resale.
>
> Kennedy's claim in this regard is that the statute is unconstitutionally vague. However, we need not reach that issue as there is simply no evidence in support of the board's finding that the public was being, or was likely to be, deceived, defrauded or harmed. Kennedy's explanation for the resale of the birth control pills was that he was required to purchase larger quantities than the Red Bird Pharmacy could handle in order to get a price his customers could afford to pay. The board offered no evidence whatsoever contradicting Kennedy's motives. There is not the slightest evidence that Kennedy personally benefited, financially or otherwise, from these transactions.

> Conceivably Kennedy was defrauding Wyeth Laboratories (although the record before the board does not establish the elements of fraud), or perhaps his conduct constituted a breach of his contract with that firm. But Wyeth did not participate in the hearing. As far as we know, Wyeth has never lodged any complaint against Kennedy before any tribunal, administrative or judicial. In any event Kennedy's actions vis a vis Wyeth did not amount to unprofessional conduct as contemplated by the legislature in KRS 315.121(1)(f). Never was the conduct of reselling the birth control pills to another drug company shown to deceive, defraud or harm the public. Such a showing is essential, we believe, to any charge of unprofessional conduct, again by reference to the plain words of the statute.

The court reversed the circuit court's decision and remanded the case back to the board of pharmacy for dismissal of the charges.

Notes on Kennedy v. Kentucky Board of Pharmacy

1. The PDMA prohibits the resale of prescription drugs by hospitals, except under specified circumstances. It would appear that Kennedy violated the PDMA because reselling to a wholesaler is not one of the specified exceptions. Drug returns are not considered a sale or trade for the purpose of the PDMA, but Kennedy was not engaging in product returns. Although Kennedy appeared to be acting with no intent to profit from the resale, the PDMA does not include profit as a criterion. The PDMA was enacted to invalidate this type of situation and prevent a secondary distribution market. As this case demonstrates, state law was inadequate, and Kennedy may have been fortunate that the FDA did not bring the action.
2. Notice that the state law provides that a wholesaler is any person except a pharmacist. Could a pharmacist thus ever be considered a wholesaler under Kentucky law? Moreover, the statute says a wholesaler is a person who buys the drugs for resale. Was Kennedy buying the drugs originally for resale? He admitted that he purchased more product than necessary in order to get the best price. What else could he do with the excess other than resell? State boards have historically used unprofessional conduct charges as a catchall for acts that the board deems offensive but that the law does not specifically prohibit.
3. In Kennedy's defense, the PDMA was intended to prevent drug diversion because of fear of adulterated and misbranded products and unfair competition. None of these problems would seem to be outcomes from Kennedy's resale. However, violation of the PDMA does not require proof of injury or bad consequences.

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