



# *Pharmaceutical Compounding or Pharmaceutical Manufacturing?*

A REGULATORY PERSPECTIVE

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## ABSTRACT

At one time, nearly all prescriptions were compounded preparations. There is an ongoing demand for compounded prescription medications because manufacturers cannot fulfill the needs of all individual patients. Compounding pharmacies are a long standing yet less frequently discussed element in the complex matrix of prescription drug manufacturing, distribution, and patient use. The drug shortage situation for many necessary and life-saving drug products is a complicating factor that has led to the numerous quality issues that currently plague large-scale compounding pharmacies. The states are the primary regulator of pharmacies, including community drug stores, large chains, and specialty pharmacies. Pharmacies making and distributing drugs in a way that is outside the bounds of traditional pharmacy compounding are of great concern to the U.S. Food and Drug Administration. The U.S. Congress has recently passed the Drug Quality and Security Act. This legislation establishes a clear boundary between traditional compounders and compounding manufacturers. It clarifies a national, uniform set of rules for compounding manufacturers while preserving the states' primary role in traditional pharmacy regulation. It clarifies the U.S. Food and Drug Administration's authority over the compounding of human drugs while requiring the Agency to engage and coordinate with states to ensure the safety of compounded drugs.

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Pharmacy compounding is a vital service that helps many people and serves an important public health need for patients who cannot be treated with a U.S. Food and Drug Administration (FDA)-approved medication.

Pharmacy compounding is the art and science of preparing personalized medications for patients. Compounded medications are generally made from scratch, and individual ingredients are mixed together in the exact strength and dosage form required by the patient. Also, commercially available dosage forms may sometimes be modified to better fit the dosing needs of an individual. These operations are performed by a licensed pharmacist in response to a prescription written by a licensed physician based on the medical needs of an individual

patient. Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

While this paper discusses compounding and manufacturing with respect to preparations for human applications, much of this information is also applicable to veterinary drugs. The individual states and FDA authority extend to veterinary drugs in addition to human drugs. FDA regulates compounding of veterinary drugs through the application of the Extra-Label Drug Use (ELU) rules recited in 21 United States Code of Federal Regulations (CFR) 530.13<sup>1</sup> and its *Compliance Policy Guide* (CPG 608.400).<sup>2</sup>

## HISTORY

Compounding of medicines can be traced back to ancient times with compounding pharmacies existing for thousands of years in some form. The Middle East purportedly had the first pharmacy in Baghdad in the first century A.D.; alchemy and compounding were used.<sup>3,4</sup>

Compounding pharmacies have been in America since the early 19th century. Compounding pharmacies of the 1800s gave way to the modern pharmaceutical industry.



**TYPICAL AMERICAN DRUG STORE WITH A SODA FOUNTAIN, AROUND 1905**

Pharmacist owners of the past like Merck and Dohme from Merck Sharp and Dohme; Ely Lilly; Warner; Lambert; Smith of Smith Kline; and French Labs went on to be manufacturers making many of the commercial medications we have today.<sup>5</sup>

With the advent of mass drug manufacturing in the 1950s and 1960s, compounding rapidly declined. The pharmacist's role as a preparer of medications evolved to primarily that of a dispenser of manufactured dosage forms. However, this one-size-fits-all nature of many mass-produced medications meant that some patients' needs were not being met.

## CURRENT ENVIRONMENT

Today, there is an ongoing demand for compounded prescription medications because manufacturers cannot fulfill the needs of all individual patients. The drug shortage situation for many necessary and life-saving drug products is a complicating factor that has led to the numerous quality issues that currently plague large scale compounding pharmacies. In particular, the generic injectable preparations are a major source of concern. Also, with the concept of personalized medicines gaining popularity, many physicians are seeing the benefit of custom compounded preparations and adding them to their daily prescription protocols.

The modern compounded prescription is typically defined as being for a single, individual patient only. The most common modern day preparations are for:

- Patients requiring limited dosage strengths, such as children or infants
- Patients requiring a different formulation, such as turning a tablet into a liquid or topical ointment or cream
- Patients requiring an allergen-free medication
- Patients who absorb or excrete medications abnormally
- Patients who need drugs that have been discontinued by pharmaceutical manufacturers
- Patients facing a supply shortage of their normal drug
- Individuals who may require flavored additives in preparations

## STATES REGULATORY STATUS

The states are the primary regulator of pharmacies, including community drug stores, large chains, and specialty pharmacies. The practice of pharmacy, including the licensing of individual pharmacists and pharmacies, is regulated by a State Board of Pharmacy which has the primary responsibility for day-to-day oversight. Under current regulations, there is no differentiation between licensed pharmacists and pharmacies that simply dispense commercially manufactured pharmaceutical prepa-

rations made by large-scale pharmaceutical companies and those that prepare specially compounded preparations based on personalized prescriptions.

State laws are passed by the state legislature and then the state executive agencies, in this case the Boards of Pharmacy, write the rules or regulations that serve to govern the practice of pharmacy. These state rules are updated periodically by the individual State Boards of Pharmacy, which operate in the 50 states. Some of these practice

requirements have origins dating back 30 to 50 years when large drug manufacturers played a much smaller role as the source of medications. These laws and regulations address pharmacy standards and requirements, including items such as required licenses for each facility and for the credentialed pharmacists and other employees who work there. Also, there are require-

ments for recordkeeping, the forms used for patient prescriptions, labeling, and safety protocols related to the origin, authenticity, chain of custody, beyond-use dates of preparations, and their purity, sterility, and storage. This includes the extra, explicit authority granted to compound or mix pharmaceutical ingredients into a patient-ready preparation.

Some state's Board of Pharmacy Regulations are fairly vague on the topic of compounding, only stating in broad terms that it is a pharmacist's responsibility. Other states have more detailed compounding requirements. Since 2011, at least 16 states enacted laws affecting the practices of compounding pharmacies.<sup>6</sup>

## U.S. FOOD AND DRUG ADMINISTRATION

Since states have historically regulated the practice of pharmacy, the FDA did not require that compounded drugs be subjected to the new drug approval process. In 1992, reacting to concerns that compounding was being used to circumvent the new drug approval process for the manufacture of drugs, the FDA issued their *Compliance Policy Guide* (CPG 460.200) for industry and staff on pharmacy compounding.<sup>7</sup>

In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA),<sup>8</sup> which placed some of the policies in this compliance policy guide into law. In 2002, The United States Supreme Court invalidated FDAMA, including the provisions that placed limitations on pharmacy compounding.<sup>9</sup> As a result, in 2002, the FDA re-issued CPG 460.200 to announce how it intended to approach the regulation of pharmacy compounding and described its policy with respect to taking an enforcement action for a compounding pharmacy. This policy was tested by the federal courts in 2005 when the 3rd Circuit Court of Appeals held that all pharmacies were subject to FDA inspection with the exception of examining the books and records of the pharmacy.<sup>10</sup> The next legal challenge came in 2005 when 10 compounding pharmacies sued the FDA claiming that compounded drugs did not constitute new drugs. The 5th Circuit Court of Appeals held that compounded drugs are new drugs, but that they are exempt from the new drug approval process if, and only if, they meet the criteria outlined in FDAMA.<sup>11</sup> What resulted was a split in the circuit courts of appeal, which created tension and inconsistency in the legal standards available to the FDA for how to regulate compounded drugs.

Until now, compounding pharmacies have not been required to register with the FDA. Therefore, they did not need to tell the FDA what drugs they were making or how, even though their operations may have appeared more consistent with those of large-scale drug manufacturers than with those of traditional pharmacies. Compounded medications are not FDA approved. This means that the FDA has not verified their quality, safety, and effectiveness. Poor compounding practices can result in contamination or in medications that don't possess the strength, quality, and purity required.

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Pharmacies making and distributing drugs in a way that is outside the bounds of traditional pharmacy compounding are of great concern to the FDA. Compounding pharmacies are a long standing yet less frequently discussed element in the complex matrix of prescription drug manufacturing, distribution, and patient use. Generally, the FDA will continue to defer to state authorities regarding less significant issues related to pharmacy compounding of human drugs. However, the FDA expects that, in such cases where more serious quality or safety situations occur, cooperative efforts will result in coordinated investigations, referrals, and follow-up actions by the states.

When the scope and nature of a pharmacy's activities raise concerns normally associated with a drug manufacturer and result in significant violations of the new drug,

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adulteration, or misbranding provisions of the Food Drug and Cosmetic Act (FD&C Act),<sup>12</sup> the FDA will consider enforcement action. In determining whether to initiate

such an action, the FDA must consider whether the pharmacy engages in any of the following acts<sup>6,13</sup>:

- Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions
- Compounding drugs that were withdrawn or removed from the market for safety reasons
- Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned Investigational New Drug application (IND) in accordance with CFR Title 21 Part 355(i) and CFR Title 21 Part 312
- Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility. *Note: Bulk drug substance, as defined in CFR Title 21 Part 207.3(a)(4), means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug; the term does not include intermediates used in the synthesis of such substances.*



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- Using commercial-scale manufacturing or testing equipment for compounding drug products
- Compounding drugs for third parties who resell to individual patients or offering compounded drug preparations at wholesale to other state-licensed persons or commercial entities for resale
- Compounding drug preparations that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. *Note: In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, the FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.*
- Failing to operate in conformance with applicable state law regulating the practice of pharmacy

## PHARMACEUTICAL MANUFACTURING

The 1906 Food and Drugs Act<sup>14</sup> prohibited the adulteration or misbranding of pharmaceuticals, but that law did not require premarket approval of drugs. As long as drugs were properly labeled and conformed to the applicable standard compendia, the *United States Pharmacopoeia (USP)* or the *National Formulary (NF)*, there was no federal statute to prevent their commercialization, safe or hazardous, effective or useless.

As a result of the sulfanilamide incident in 1937<sup>15</sup> that resulted in the deaths of over 100 individuals, the FD&C Act was enacted in June 1938.<sup>16</sup> This Act revamped the oversight of food and drugs and included for the first time consumer protection over medical devices and cosmetics. The foundation of the drug provisions of this new law required manufacturers to submit to the FDA evidence of a drug's safety before it could go on the market. In addition to reports of the drug's safety, the applicant also needed to provide a statement of the drug's composition and a description of methods, facilities, and controls used in its production. The FDA had two months to approve, reject, or request additional data from the firm. This mandate for premarket evidence of a drug's safety represented the birth of the New Drug Application (NDA).

In 1962, Congress amended the drug provisions of the law to require that manufacturers establish not only the safety but also the efficacy of the drug through adequate and well-controlled clinical trials prior to marketing. The amendment also formalized good manufacturing practices.<sup>17</sup>

Today, current good manufacturing practices that the FDA uses to regulate the manufacturing practices for the preparation of human and animal drugs are found in 21 CFR 210 & 211. These regulations cover all aspects of the preparation of drug products from raw materials to end-product testing for release, and are inclusive of building and facilities (e.g., design, construction, lighting, maintenance, sanitation), personnel qualifications, receipt and testing of materials, manufacturing procedures, and packaging and distribution of the finished commercial dosage form. Pharmaceutical manufacturers are expected to comply with these rules and regulations. Pharmaceutical manufacturers are required to demonstrate a product's safety, efficacy, and quality throughout the product's shelf life before the FDA will grant them the ability to sell the product in interstate commerce. The regulations that govern the content of a NDA, including the comprehensive product quality information, and the process for approval are found in 21 CFR. 314. And, from time to time, the FDA may choose to issue guidance for regulated industry to announce the FDA's current thinking on various policy topics related to the development and manufacture of drug substance and drug products.



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## PHARMACEUTICAL COMPOUNDING ISSUES

A number of issues<sup>18</sup> have emerged in recent years (concerning the safety of compounded preparations) that have added to the question of compounding versus manufacturing. These are:

- Is it clear which compounded drug orders meet the state-regulated standards and which cross into a manufacturing regulatory category?
- Are there uniform and up-to-date definitions of compounding, wholesale, specialty, and hospital-based pharmacies?
- Is there clear language about sterile and nonsterile compounding? *Note: Single-use injectable vials are sometimes over filled and have no preservative added. This makes costs higher, while repeat-injection use by some providers brings additional dangers of contamination and infection.*
- With regard to inspection of facilities; how often, by whom, under what conditions? What kind of independent accreditation or evaluation is in place?
- Which agencies or boards, state or federal, take action when violations or omissions occur?
- What levels of penalties are in place? Who can order the closure of an operating pharmacy?
- Inspection and enforcement agencies have varied levels of budgets and personnel to complete inspections and enforcement. What level of funding needs to be in place and where does it come from?
- Are records of inspections publicly or adequately available to policymakers and federal and state regulatory entities?

Some recent adverse event reports received by the FDA associated with compounded medications, which have provided impetus for both state and the federal government to take a closer look at pharmacy compounding, are highlighted. For a more complete list, one can visit the FDA website on pharmacy compounding.<sup>19</sup>

- In August 2011,<sup>20</sup> the FDA alerted healthcare professionals that repackaged injections of Avastin (bevacizumab) caused serious eye infections in the Miami area. A pharmacy had repackaged the Avastin from single-use vials into single-use syringes, distributing them to multiple eye clinics. At least 12 patients developed eye infections; some lost the remaining vision in the eye being treated.
- From November 2011 to April 2012,<sup>21</sup> 33 eye-surgery patients in seven states suffered a rare fungal eye infection tied to injectable drug preparations made by a compounding pharmacy in Ocala, Florida. Most of those patients suffered partial to severe vision loss.
- The Fall 2012 outbreak of fungal meningitis<sup>22</sup> has been linked to an injectable steroid medication prepared by a firm in Framingham, Massachusetts. Hundreds of people across the country have been infected with serious injuries and deaths reported.

In April 2013, the FDA announced that as a result of a priority inspection program,<sup>23</sup> federal regulators found numerous unsafe practices at 31 compounding pharmacies located in 18 states. Observations concerning sterility practices, inappropriate conditions for sterile processing, and other practices that create risk of contamination were noted. All but one pharmacy that was inspected received an inspection observation report (FDA Form 483) that lists objectionable conditions observed at the facilities. The one firm that did not receive a FDA Form 483 was not preparing sterile drugs. Some of the problems found included unidentified black particles floating in vials of sterile medicine; rust and mold in cleanrooms where sterile injectable medications were manufactured; employees wearing nonsterile lab coats and handling sterile preparations with bare hands.

## THE FUTURE FOR PHARMACY COMPOUNDING

As a result of the many negative recent events involving pharmacy compounding, the FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violate the FD&C Act.

Some compounding pharmacies have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies. They have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. However, the practices of many of these

entities are more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. Some firms receive and use large quantities of bulk drug substances to “manufacture” large quantities of drug “products” in advance of receiving a valid prescription for them. Some firms sell to physicians and patients with whom they have only a remote relationship.

Recently, the FDA met with state regulators to discuss the future course of compounding pharmacy regulations.<sup>18</sup> From their collective perspectives, there appears to be a regulatory vacuum with respect to the non-traditional compounding pharmacies. Also, there is a concern about the adequacy of state regulation of compounding pharmacies in a more general sense.

The U.S. Congress has recently passed and the President signed into law, the Drug Quality and Security Act.<sup>24</sup> This legislation

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establishes a clear boundary between traditional compounders and compounding manufacturers. It clarifies a national, uniform set of rules for compounding manufacturers while preserving the states' primary role in traditional pharmacy regulation. It clarifies the FDA's authority over the compounding of human drugs while requiring the Agency to engage and coordinate with states to ensure the safety of compounded drugs.

The legislation draws a distinction between traditional compounding pharmacies and those making large volumes of compounded drugs without individual prescriptions.<sup>25</sup> These larger organizations, to be known as *outsourcing facilities*, will be regulated by the FDA. Traditional compounding pharmacies will continue to be regulated by state boards of pharmacy. Compounding pharmacies that practice outside the scope of traditional pharmacy practice need to register as an outsourcing facility that would be subject to FDA oversight in much the same way as traditional pharmaceutical manufacturers. Patients and providers would have the ability to purchase preparations from outsourcing facilities that comply with FDA quality standards. This legislation also bans compounding pharmacies from essentially making a copy of an approved and marketed drug product.

The key aspects of this legislation for compounding are:

- Preserve and protect the practice of traditional pharmacy compounding occurring in community pharmacies
- Voluntary federal registration as an outsourcing facility for compounding
- Beginning in 2015, a registration fee of \$15,000 and an additional

\$15,000 (inflation adjusted) for inspections will be assessed on outsourcing facilities.

- A list will be developed of drugs for which compounding at an outsourcing facility is to be avoided.
- Compounded drugs from outsourced facilities will have a label saying this is a compounded drug or equivalent lan-



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guage. The FDA will list the regulated outsourcing facilities on their website.

- Eliminate the unconstitutional provisions of the FD&C Act that created uncertainty regarding the laws governing compounding and require the FDA to engage in a two-way communication with the states

- The FDA's role in oversight of these outsourcing facilities is clarified. The FDA will, in theory, know who the outsourcers are and what they are making, receive adverse event reports about compounded drugs, and have the authority to conduct facility inspections.

## NEW U.S. FOOD AND DRUG ADMINISTRATION GUIDANCES ON PHARMACY COMPOUNDING

As a consequence of this legislation, the FDA released three draft guidance documents intended to clarify its role in regulating pharmacy compounding.<sup>26</sup> The three draft guidance documents are relatively short and cover three distinct topics:

- Who is regulated by Section 503A of the FD&C Act?
- Who needs to register as an outsourcing facility under Section 503B of the FD&C Act?
- Interim product reporting by outsourcing facilities and which information must be submitted under Section 503B of the FD&C Act.

In the guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*,<sup>27</sup> the FDA clarifies the conditions under which a compounded prescription must be prepared in order to be exempt from other relevant provisions of federal law. Specifically, the drug preparation must:

- Be made for an individual, identified patient based on a valid prescription by a practitioner
- Be made by a licensed pharmacist in a state or federal licensed facility or by a licensed individual physician
- Be compounded in compliance with *USP-NF* standards using drug substance and other ingredients in compliance with an established compendia monograph, if available, or other FDA manufacturing requirements

- Be accompanied by valid certificates of analysis
- Not be a compounded version of a drug that has been withdrawn from the market due to reasons of safety or efficacy
- Not be a preparation identified by the FDA as being unsuitable for compounding
- Not be an exact copy of a commercially available drug product

Drug preparations may be compounded in limited quantities prior to the receipt of a prescription provided the pharmacy has historically received valid orders for the preparation. Compounded drug preparations will be subject to quality standards. A failure to meet these standards will subject the compounder and its preparations to regulatory enforcement by the FDA and federal authorities.

The second draft guidance, *Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, reflects a new category of outsourcing facilities.<sup>28</sup> These facilities will be inspected by FDA regulators similarly to conventional pharmaceutical manufacturers and must comply with current Good Manufacturing Practices.<sup>29</sup> Outsourcing facilities must register with the FDA annually between October 1 and December 31 and must indicate whether it intends to compound, within the next calendar year, a drug that appears on the FDA's drug shortage list. Also, it must indicate if it compounds from bulk drug substances and, if

so, whether it compounds sterile drug preparations. In addition, companies need to provide information about the location and address of each facility, as well as a unique facility identifier.

A third draft guidance document, *Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*,<sup>30</sup> outlines the requirements for outsourcing facilities. In particular, the guidance clarifies that outsourcing facilities under 503B of the FD&C Act must submit to the FDA a list of all drug preparations compounded by the facility during the previous six-month period. The list must be submitted twice per year, in June and December.

Each submission must contain specific information:

- The active ingredient and strength of active ingredient per unit
- The source of the active ingredient (bulk or finished drug)
- The NDC number of the source drug or bulk active ingredient, if available
- The dosage form and route of administration
- The package description
- The number of individual units produced
- The NDC number of the final preparation, if assigned

Reports should be made through the FDA's electronic drug registration and listing service in structured product labeling (SPL) format.

## PHARMACY COMPOUNDING ASSOCIATIONS

As a consequence of the past safety and quality issues pertaining to pharmacy compounding, some of the nation's leading pharmacy organizations have joined together to create the Pharmacy Compounding Accreditation Board (PCAB; <http://www.pcab.org/>). This is a voluntary quality accreditation designation for the pharmaceutical compounding industry. It is a mechanism to allow compounding pharmacists to let the public know that they are producing a high-quality compounded medication. PCAB accreditation gives patients, prescribers, and payers a way to select a pharmacy that meets or exceeds *USP's* high-quality standards.

There is also the International Academy of Compounding Pharmacists (IACP; <http://www.iacprx.org/>), an association which represents pharmacists, technicians, students, and other members whose focus is on the specialty practice of pharmacy compounding.

In addition, with the changes to be implemented regarding large-scale pharmacy compounding, there are organizations<sup>31,32</sup> which can provide ready-made policies and procedures that follow the standards of the *USP*, PCAB, and the FDA, allowing compounding pharmacies to ensure that they meet and are in compliance with current state and federal requirements.

## PATIENT CONSIDERATIONS

The issue of pharmaceutical compounding versus pharmaceutical manufacturing has become a complex one that has prompted legislators at the state and federal levels to take action. Over the years, pharmacy compounding, as originally practiced and defined by state pharmacy regulations, has changed significantly. Historically, a doctor or other legally authorized prescribers, wrote a prescription for a patient with special needs, and the pharmacist prepared a suitable dosage form to meet the individual patient's requirements. In today's environment, this may no longer be an accurate description of pharmacy compounding. In some cases, it has evolved into a more complex large-scale, manufacturing-type operation. This has prompted State and Federal Governments to redefine pharmacy compounding and to update laws and regulations governing it.

Patients must still rely on the expertise of the individual pharmacist who prepares this medicament for its quality, safety, and effectiveness. It is the pharmacist's responsibility to ensure that all state and federal requirements are met in filling a legal prescription, whether it simply consists of dispensing a pre-prepared commercial dosage form or a compounded medicament individualized for a specific patient.

The following are some tips for patients<sup>33</sup> regarding compounded medications, the information of which can be provided to the patients by the compounding pharmacist:

- Ask your doctor if an FDA-approved drug is available and appropriate for your treatment.
- Check with the pharmacist to see if he or she is familiar with compounding the preparation in your prescription, and whether he or she has the training, equipment, and processes in place to compound that preparation.
- Get information from your doctor or pharmacist about proper use and storage of the compounded preparation.
- If you receive a compounded drug, ask the pharmacist if your doctor asked for it to be compounded.
- If you experience any problems or adverse events, contact your doctor or pharmacist immediately.
- Report any adverse events experienced while using the preparation to FDA's MedWatch program.<sup>34</sup>

## CONCLUSIONS

Compounding of medications is an important part of the practice of the pharmacy profession. A pharmacist has the responsibility to

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ensure that compounded medications are of suitable quality, safety, and efficacy.

As stated previously, until now, compounding pharmacies have not been required to register with the FDA nor were they required to inform the FDA what drugs they were making or how. Because compounded medications do not have FDA approval, their quality, safety, and effectiveness cannot be verified.

Compounding pharmacies must now ensure that they comply with the recently implemented federal legislation. The FDA expects that, in such cases where serious quality or safety situations occur, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions. When the scope and nature of a pharmacy's activities raise concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act, the FDA will consider enforcement action.

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