

American Pharmaceutical Association

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PHARMACY COMPOUNDING: FDA REGULATORY POLICY

*Jane Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research, FDA*

Slide 1

I'm delighted to be here in Seattle to participate in this discussion on pharmacy compounding. I know this is a very important topic to APhA members, and it is one that I, personally, have spent a great deal of time grappling with.

Slide 2 - Regulatory Issues

Pharmacy compounding poses some of the toughest regulatory issues I have had to face in my almost 30 years in government. It raises questions of Federal vs State roles, the role of regulatory agencies in individuals lives

and livelihoods, the role of the Federal government in the provision of healthcare, and even, as we found out when the FDA Modernization Act was passed, constitutional questions!

SLIDE 3 – Objectives

Today I'm going to help you to better understand the Federal legal framework for the regulation of drugs and the evolution of FDA's regulatory policies on pharmacy compounding. I will explain why FDA has concerns about certain types of pharmacy compounding that go beyond the regular course of the practice of pharmacy and explain FDA's current thinking about the factors we will consider in determining whether to take enforcement action against inappropriate pharmacy compounding.

SLIDE 4: Federal Legal Framework

I'll begin with a very broad overview of the Federal legal framework for the regulation of human drugs in the United States. Under the Federal Food, Drug, and Cosmetic Act, all new drugs must demonstrate that they are safe and effective and be approved under a new or abbreviated new drug application. Drug is defined broadly to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease."

Under the law, drugs may not be adulterated or misbranded. That is, the drugs must be made in conformity with good manufacturing practices to assure that they meet the Act's requirements as to safety and have the quality and purity characteristics they are represented to possess. All drugs must be properly labeled, and a drug's labeling may not be false or misleading in any particular, or the drug is misbranded.

While some may question whether the requirements of section 505 regarding approval of new drugs apply to compounded drugs, FDA continues to take the position that all compounded drugs are subject to section 505 unless FDA exercises enforcement discretion to allow compounding without an approved new or abbreviated new drug application, although we do not believe regulating through the exercise of enforcement discretion is the best way to regulate.

SLIDE 5: COMPOUNDED DRUG REQUIREMENTS

In addition, FDA maintains that other statutory provisions apply to compounded drugs as they do to all drugs including:

- Promotional statements and labeling must be truthful and not misleading

- Compounded products must have the strength, quality and purity that they purport to have
- Active pharmaceutical ingredients, also referred to as bulk drug substances, must have been manufactured at a facility that is registered with FDA and the ingredient must be listed with FDA

SLIDE 6: COMPOUNDING REQUIREMENTS CONT'D

- Compounded product must not be dangerous to health as labeled, and
- Compounded drug product must have adequate warnings.

This is the Federal legal framework from which we approach how to address pharmacy compounding. FDA cannot promulgate regulations exempting pharmacy compounding from these statutory requirements. Instead, we must exercise enforcement discretion to allow

appropriate pharmacy compounding while trying to curb what we consider to be abuses that could harm patients or undermine the new drug approval process on which patients have come to depend to ensure the safety and effectiveness of their medications.

SLIDE 7: CHARACTERISTICS OF TRADITIONAL PHARMACY COMPOUNDING

FDA's regulation of pharmacy compounding can be characterized as attempting to distinguish acceptable from unacceptable practices. Unfortunately, these practices do not lend themselves to black and white definitions. On the one hand are pharmacists who compound reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. Often, these pharmacists work in communities alongside physicians who write prescriptions

for compounded medications to meet the needs of an individual patient. Such compounding is usually performed at the pharmacy site for prompt dispensing or administration to a patient. The pharmacist directly interacts with the patient and is available to advise patients on the characteristics and use of a compounded medication. Based on this relationship between the pharmacist and the patient, the pharmacist may monitor a patient's reaction to a compounded medication and may facilitate the patient's prompt communication with a physician regarding any adverse reactions.

SLIDE 8: Non-Traditional Pharmacy Compounding

On the other hand are companies that manufacture excessive quantities of unapproved drugs in advance of or totally without receiving a valid prescription for them, or copy commercially available products when there is no

medical need for a compounded product. These pharmacies may have little or no direct interaction with patients or their physicians. Sometimes, the doctor may not even be aware a compounded drug is being used to fill a prescription. In some cases, the scale of these operations is indistinguishable from small drug manufacturers. Some pharmacists have been found to compound drugs that are contaminated or that are dangerously subpotent or superpotent in a manner that can threaten public health.

But, as I indicated, these two operations lie on a continuum of operations. The difficulty is trying to secure the ability of those doing legitimate compounding while discouraging practices that we believe should be done under a new drug application.

SLIDE 9: FDAMA

In 1997, Congress enacted legislation in the Food and Drug Administration Modernization Act that was designed to better help us draw the line between acceptable pharmacy compounding and unacceptable compounding that looked more like manufacturing. Under section 503A of the Act, drug products that were compounded by a pharmacist or physician on a customized basis for an individual patient were entitled to exemptions from three key provisions of the Act:

(1) the adulteration provision of section 501(a)(2)(B) concerning the good manufacturing practice requirements,

(2) the misbranding provision of section 502(f)(1), concerning the labeling of drugs with adequate directions for use, and

(3) the new drug provision of section 505, concerning the approval of drugs under new drug or abbreviated new drug applications.

To qualify for these exemptions, a compounded drug product was required to satisfy several requirements, some of which were to be the subject of FDA rulemaking or other actions.

SLIDE 10: WESTERN STATES

These exemptions were overturned by the Supreme Court in April, 2002 in Western States Medical Center v. Shalala. In its decision, the court found that section 503A contained unconstitutional restrictions on commercial speech and let stand the lower court holding that these restrictions could not be severed from the rest of section 503A, rendering invalid all of the remaining provisions of section 503A.

SLIDE 11: WESTERN STATES, CONT'D

However, the Court's decision contained provisions that endorsed some of FDA's approach to the regulation of pharmacy compounding. The Court recognized that the Federal government needs to be able to distinguish small-scale compounding from larger scale manufacturing activities and the Court specifically identified factors in the 1992 Compliance Policy Guide that did not restrict speech as a potential way to draw those distinctions. In addition, the Court explicitly affirmed that it was clearly an important Federal government interest in regulating pharmacy compounding to take steps to preserve the effectiveness and integrity of the new drug approval process.

SLIDE 12: THE COMPLIANCE POLICY GUIDE

As I'm sure you are all aware, on June 7, 2002, only a few weeks after the Supreme Court's decision, FDA

issued a Compliance Policy Guide on pharmacy compounding that described the factors the Agency would consider in determining whether to take enforcement action against compounding that raised the kinds of concerns normally associated with a drug manufacturer and resulted in significant violations of the new drug, adulteration, or misbranding provisions.

Although the guidance took effect immediately, we solicited comments on the guidance and we received thoughtful comments from many of our pharmacy compounding stakeholders, including APhA.

We have carefully considered the comments submitted and we are revising the Guide. We intend to issue a new draft for public comment, and will hold a public meeting, that I will tell you about later.

In the remainder of my talk, I would like to share with you our current thinking about the revisions we are proposing to make. The new draft document is currently in clearance and what I will tell you today must be viewed as very preliminary and may not reflect the contents of the draft when it is issued.

SLIDE 13: THE NEW COMPLIANCE POLICY GUIDE

Many of the comments suggested that the June 2002 CPG purported to distinguish compounding from manufacturing but, in fact, the factors in the June CPG actually dealt with inappropriate compounding that would not be considered manufacturing. The new draft Compliance Policy Guide is likely to separate and more clearly identify those factors that pertain to distinguishing manufacturing from compounding. Such factors may include:

- Producing drugs outside of the traditional patient-physician-pharmacist relationship
- Producing drugs in anticipation of receiving prescriptions, except in limited quantities
- Producing drugs for third parties for resale or producing drugs for wholesale distribution
- Using industrial scale manufacturing equipment
- Copying commercially available products.

Also in response to comments, the revised CPG is also likely to clarify several of the factors such as those pertaining to industrial scale equipment, on which we received a lot of comments, and what constitutes legitimate compounding for office stock.

**SLIDE 14: NEW COMPLIANCE POLICY GUIDE,
CONT'D Industrial scale equipment**

We have considered many different examples of what we would consider to be industrial scale equipment such as an automatic or semi-automatic encapsulating machine that is capable of producing thousands of capsules per hour, or an automatic fill machine that is capable of filling, labeling, and sealing thousands of nebulizer doses per hour. Contrast this equipment with items such as a hand blender, a hand-operated single punch tablet press, or a desk top capsule machine capable of producing no more than a few hundred capsules per hour. We hope that by including specific examples, we can clarify what we consider industrial scale equipment. We do intend to look at all of the circumstances surrounding the compounding include the total volume produced, the equipment used, and the existence of the patient, physician, pharmacist relationship.

SLIDE 15 – OFFICE STOCK

Related to this, we may try to address questions that have arisen concerning when compounding for office stock may be considered legitimate pharmacy compounding. We have encountered situations where pharmacies have set up what we consider to be manufacturing facilities, making large quantities of unapproved drugs without prescriptions and shipping them to doctor's offices or to wholesalers for resale to doctor's offices as "office stock." Again, the question is where do we draw the line between legitimate pharmacy compounding, and manufacturing operations.

We recognize that when a drug is compounded for office stock a prescription is unlikely to be received in advance of compounding the product. We are thinking about defining *office stock drugs* as those that are

compounded in limited quantities for distribution to a health practitioner authorized to prescribe drugs for subsequent administration to patients by a health practitioner authorized to administer drugs. To ensure that office stock products are clearly delineated, we would like to see them labeled as "For Office Use Only" and "Not for Resale." We also feel that office stock compounding should be appropriate only in those states that permit compounding for office stock.

SLIDE 16: OTHER CONSIDERATIONS THAT COULD RESULT IN ENFORCMENT ACTION

After we separated out the factors that we would use to distinguish compounding from manufacturing, we were left with the question of whether we might take action against pharmacy compounding that did not rise to the

level of manufacturing, and if so, under what circumstances.

We have always acknowledged the role of the States in the regulation of pharmacy compounding and we intend to continue to refer complaints to the States, provide support to the States upon request, and cooperate in investigations and necessary follow-up action. But we can contemplate situations in which States may request our help for situations involving compounding that does not rise to the level of manufacturing. For example, we cooperated with the State of California in the investigation of the Doc's pharmacy situation and we cooperated with the State of North Carolina in investigating the Urgent Care case.

As I described at the beginning of my talk, there are sections of the Act that apply to all drugs, even

compounded drugs, including certain labeling and misbranding provisions and some of the adulteration provisions. We can contemplate situations in which FDA enforcement action would be appropriate with regard to these and other provisions. We feel we must reserve the right to take enforcement action if we become aware of pharmacy compounding that could have an adverse effect on public health or that threatens the integrity of the drug approval process.

For example, FDA might be in the best position to take action if a drug that is being compounded is being made from inappropriate active ingredients. Drugs that are compounded with inherently unsafe or poor quality ingredients could threaten public health. Drugs that are used in compounding should either be components of FDA-approved drugs, or in compliance with a current USP

monograph for the ingredient. Others on this panel will be discussing the importance of developing quality standards for pharmacy compounding and we would like to work with you in this effort.

SLIDE 17: NEXT STEPS

Some of you may be saying this is the same old /same old FDA approach. We hope you'll reserve judgment until you see the new draft of the Compliance Policy Guide. We intend to issue a new draft for public comment, and we plan to hold a public meeting on June 23 to obtain further public input. This will be an interactive session. We will have an FDA panel that will actively question participants so that we will fully understand the concerns expressed. We hope you will take this opportunity to have a dialogue with us on the development of our regulatory policies towards pharmacy compounding.

After the meeting, and after the comment period closes, we will revise the guidance as appropriate and issue a final guidance.

I would be remiss if I didn't mention possible legislative initiatives. As many of you know, the Senate HELP committee held a hearing on pharmacy compounding last fall. FDA representatives, as well as APhA representatives testified at the hearing and have responded to followup questions. Some of the questions mentioned the possibility of new legislation on pharmacy compounding. The Administration does not now have a proposal for legislation but, of course, we would be willing to work with Congress and other interested parties if Congress decided to take up a pharmacy compounding bill.

That concludes my remarks. Thank you again for
inviting me to speak.