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FEDERAL AND STATE ROLE IN PHARMACY COMPOUNDING AND RECONSTITUTION: EXPLORING THE RIGHT MIX TO PROTECT PATIENTS

HEARING

BEFORE THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

FIRST SESSION

ON

EXAMINING STATE AND FEDERAL OVERSIGHT TO ENSURE THE SAFETY AND QUALITY OF DRUG COMPOUNDING—THE PROCESS OF MIXING, COMBINING, OR ALTERING INGREDIENTS TO CREATE A CUSTOMIZED MEDICATION FOR AN INDIVIDUAL PATIENT—BY PHARMACIES

OCTOBER 23, 2003

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FEDERAL AND STATE ROLE IN PHARMACY COMPOUNDING AND RECONSTITUTION: EXPLORING THE RIGHT MIX TO PROTECT PATIENTS

THURSDAY, OCTOBER 23, 2003

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10 a.m., in Room 430, Dirksen Senate Office Building, Senator Bond, presiding.

Present: Senators Bond, Roberts, Ensign, and Reed.

Senator BOND. Good morning. The meeting of the Senate Health, Education, Labor and Pensions Committee will come to order.

This is a very busy day in the Senate, and many of my colleagues who wanted to be here have other commitments. I know Senator Roberts has a great interest in this issue. He has to be on the Floor, so I'm taking the liberty of starting ahead of his arrival. I am hoping that others will be able to join us.

But as you all know who have followed the Senate, this is a time when so many important measures are going on. There is an Environment and Public Works markup down the hall that I may have to go down to join to make a quorum, and most other members face the same challenges I do.

OPENING STATEMENT OF SENATOR BOND

Senator BOND. Today we are going to be exploring the question of Federal and State roles in pharmacy compounding and reconstitution: exploring the right mix to protect patients. When people get sick, they want to know that their medicine is safe and effective, and most importantly, they want to know that it is just what the doctor ordered. That is why we are here today.

This hearing is not intended to be an attack on the practice of compounding. The committee recognizes and appreciates the vital role that compounded drugs play in the delivery of health care. Compounding ensures that medications are available to meet many individualized patient needs. Many pediatric patients, for example, require flavoring to be added to mask the bitter taste of some medications. Some patients have difficulty swallowing a capsule and require a special dosage for them. And some patients are allergic to a preservative or dye in a manufactured product and require a dye-free or preservative-free dosage. There is no question that compounding provides patients critical access to medications that are not commercially available.

However, recent media coverage and significant adverse events have brought to our attention a significant number of very real problems caused by compounded drugs. We have received reports of nonsterile eye drops causing blindness, spinal injections contaminated with bacteria and/or fungus, resulting in hospitalization and, in some cases, death, and children poisoned as a result of pharmacy compounding errors.

Based on voluntary reporting, media reports and other sources, the Food and Drug Administration has become aware of over 200 adverse events involving 71 compounded products since about 1990. The incidence of heightened concern is about compounded drug safety and quality. Yet, when these types of tragedies occur, there are very few State laws and no Federal law requiring that the events be reported. Unlike drug manufacturers, who are required to report adverse events associated with the drugs they produce, the Food and Drug Administration does not require pharmacies or any other body to report adverse events associated with compounded drugs.

Because oversight and surveillance of pharmacy compounding at the State and Federal level is limited, at best, little is known about how widespread the practice of compounding is, the ability of States and the Federal Government to regulate compounding, and how compounding impacts public health and safety.

Today's hearing is designed to address those very important issues. As our population continues to age, and the demand for pharmaceuticals continues to grow, we have to make sure that appropriate safeguards are in place to protect patients from substandard, contaminated, subpotent or superpotent drugs, so that we can ensure the highest standard of care.

My goal, our goal, is not to federalize the oversight of pharmacies and compounding pharmacists, or institute additional needless and burdensome paperwork and regulatory requirements. But the issue at hand is clear. We have a responsibility to ensure that patients and doctors are receiving safe and accurate dosages of compounded drugs. This morning, as we examine issues surrounding pharmacy compounding, the safety of patients must always be our guiding force. I look forward to the testimony of our panels.

Before introducing the two distinguished members of the first panel, I will call on my colleague, Senator Ensign, for any comments he wishes to make.

Senator Ensign.

OPENING STATEMENT OF SENATOR ENSIGN

Senator ENSIGN. Thank you, Mr. Chairman. Thanks for bringing this important issue to light.

I wanted to share a few things with the committee, just some personal experience as a practicing veterinarian, working in the medical fields, and I have a lot of friends who are physicians.

One of the things that I hope, and you mentioned in your opening statement that you didn't want to go too far with what you are trying to do, while at the same time protecting patients, because compounding pharmacists, I believe, play a vital role in the United States. As a veterinarian, there were certain things we just could not get without compounding pharmacists. We don't want them to

get down to where they are just basically taking different things and grinding them up. I mean, they have to be able to perform the way that they were trained to perform, and in so doing, you're always going to have some problems. You can never eliminate completely—I mean, there are mistakes made sometimes and there are always bad actors, just like there are in any profession.

But what I don't want to see happen when we're doing this is for us to, as the old saying goes, "throw the baby out with the bath water." We don't want to see a very valuable profession hurt to the point where they cannot operate. As a practicing veterinarian, there were things that frankly they could perform for us that we couldn't get anyplace else. We needed that service, and physicians are the same way, especially some times when people are on the cutting edge and they develop a relationship, especially with certain compounding pharmacists that are incredibly valuable. Sometimes when drugs quit being made, that is the time when compounding pharmacists have to come into play.

I know you have had some experience with diluting drugs and things like that, and frankly, those people are in jail—and they should be. But at the same time, we don't want, at least from my perspective, I don't want us to go and have, as we do around here quite often, we have this law of unintended consequences. We have got to make sure we don't end up with that law coming into being when we're trying to fix one problem we end up causing problems in other areas.

So I appreciate you having the hearing. I won't be able to stay probably for about another 15 or 20 minutes, but I appreciate you having this hearing. Thank you.

Senator BOND. Thank you very much, Senator Ensign. We value your expertise as a practicing veterinarian. You and Senator Wayne Allard have given me very valuable medical advice when I couldn't track down Senator Frist on the Floor, to get advice. Senator Allard was the one who warned me when I had a hip replacement, that the dogs whose hips he replaced usually ran around too much and dislocated their hip, so I took that advice to heart.

Seriously, on the question in front of us, I certainly share your concerns. We don't want to make it impossible or very difficult or unduly burdensome to compound, but we had a tragedy in Kansas City where a now criminally-prosecuted convicted pharmacist produced 4,200 phony compounds. There was no regulation. Do you know how he was found? He was discovered because a drug salesman noticed that he was not buying enough drugs to be filling the prescriptions that he was writing.

Now, the free enterprise system works, but I would hate to have to rely on the drug salesmen to tell us if a compounding pharmacist is grossly in error. When it has to come from the private sector, when we can't guarantee it, that just doesn't cut it.

But we need to find out what the situation is. We have asked two expert agencies. We have witnesses today, Dr. Janet Heinrich, Director of Health Care and Public Health Issues of the U.S. General Accounting Office, and Dr. Steve Galson, Deputy Director, Center of Drug Evaluation and Research, the Food and Drug Administration.

Dr. Heinrich, would you please begin. We will make your full statements a part of the record. We appreciate your being here.

STATEMENTS OF JANET HEINRICH, DrPH, RN, DIRECTOR OF HEALTH CARE-PUBLIC HEALTH ISSUES, U.S. GENERAL ACCOUNTING OFFICE; AND STEVEN GALSON, M.D., MPH, DEPUTY DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Ms. HEINRICH. Mr. Chairman and members of the committee, I am pleased to be here today as you consider State and Federal oversight to ensure safety and quality of compounded prescription drugs.

Compounding, the process of mixing, combining or altering ingredients to create a customized medication for an individual patient is, as you say, an important part of the practice of pharmacy. It is regulated by State Pharmacy Practice Acts which are enforced by State Boards of Pharmacy.

At the Federal level, the FDA, which oversees the introduction of new drugs into the marketplace under the Food, Drug and Cosmetic Act, maintains the compounded drugs are generally subject to this Act.

The quality and extent of drug compounding have surfaced as important issues in recent years. You described several serious, adverse events in your remarks. In addition, concerns have been raised that some pharmacies are going beyond traditional drug compounding and selling large quantities of drugs without meeting safety requirements for new manufactured drugs. However, the extent of this problem is unknown.

Because of these issues, you asked us to address the actions taken or proposed by States and national pharmacy organizations that may affect State oversight of drug compounding, and to look at Federal authority and enforcement power regarding compounding drugs.

In our review, we found several efforts at the State level and among national pharmacy organizations to strengthen State oversight of compounding. We selected four States for in-depth review, based on their geographic location and variation in regulations. Actions among these States included adopting new regulations, mandatory adverse event reporting, and random testing of compounded drugs.

At the national level, industry organizations are working on standards for compounded drugs that could be adopted by States in their laws and regulations. According to experts, uniform standards could help ensure that pharmacies across States consistently produce safe quality products. While these actions have the potential to improve oversight, the ability of States to provide this oversight may be affected by available resources. State pharmacy board officials in three of the four States we reviewed reported that resources were limited for inspections.

While FDA has oversight responsibility regarding drug compounding activities, it generally relies on the States to regulate the traditional practice of pharmacy, including the compounding of drugs for the needs of individual patients.

In recent years, Congress has attempted to clarify the extent of the Federal authority and enforcement power regarding compounding, and in 1997 Congress passed a law that exempted drug compounders from key portions of the Food, Drug and Cosmetic Act, if they met certain criteria. These efforts, as you know, were nullified in 2002 when the U.S. Supreme Court struck down a portion of the law's drug compounding section as an unconstitutional restriction on commercial speech, which resulted in the entire compounding section being declared invalid.

Subsequently, FDA issued a compliance policy guide to provide the compounding industry with an explanation of its enforcement policy, which included a list of factors the agency would consider before taking enforcement actions against drug compounders.

Some representatives of the pharmacist associations and others have expressed concern that the compliance policy guide creates confusion regarding when FDA enforcement authority will be used. For example, they State that terms such as "very large quantities" are not clearly defined. On the other hand, FDA officials State that the guide allows the agency the necessary flexibility to respond to a wide variety of situations where there are public health and safety concerns.

In conclusion, at least some States are taking steps to strengthen oversight, and national organizations are developing standards that may strengthen State level efforts. However, the effectiveness of these measures is unknown, and factors such as available resources may affect the extent of oversight activities.

While FDA has authority over the safety and quality of new drugs, it generally relies on States to regulate drug compounding. Given State resources, we may need to look even more to FDA in the future.

Mr. Chairman, this completes my prepared statement. I am happy to answer any questions you or other members may have.

Senator BOND. Thank you, Dr. Heinrich.

[The prepared statement of Ms. Heinrich may be found in additional material.]

Senator BOND. We will go to Dr. Galson for his opening statement, and then we will have an opportunity for questions and answers.

Dr. GALSON. Thank you, Mr. Chairman, and members of the committee. I am Steve Galson, Captain and medical officer in the U.S. Public Health Service, and Acting Director of the Center for Drug Evaluation and Research at FDA. I am pleased to be here today to discuss the public health issues related to pharmacy compounding.

Pharmacy compounding, as you know, is the combining, mixing or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription. I have brought along some charts here, and if you look at the first one there, in the left column, you see that pharmacy compounding has obvious health benefits. The patient may have an allergy to a dye or a preservative, or the patient may be a child or an elderly individual who has difficulty swallowing. The pharmacist can convert the drug to a suspension or some other form

that is more useful to the patient. In these cases, pharmacy compounding serves a clear public health need.

On the other side of the chart, though, we have become aware of instances involving compounding in which the risks of obtaining a product of substandard quality may outweigh the benefits of obtaining the drug. These risks can include problems with quality, adverse events, and drugs that just don't work. For example, a compounded narcotic analgesic "lollipop" dispensed without the labeling packaging and other patient safety features required by the agency for that product could have posed a safety hazard to children.

In another instance, a contaminated injectable steroid drug that had been compounded by a pharmacy without adequate controls resulted in serious infections in a number of patients, one of whom died.

In addition to these cases, we have seen abuses such as large-scale drug manufacturing operating under the guise of pharmacy compounding. Sometimes compounding appears to occur for economic reasons rather than genuine medical need.

We believe that most pharmacists are well trained and well equipped to safely compound certain medications. However, in some cases, compounders may lack equipment, training, testing, or facilities to ensure the right quality of the drug. In addition, compounding large quantities of drugs and copying commercially available approved products circumvents the important public health requirements of the FDA. This type of compounding undermines the drug approval process, the evidence-based system of drug review that consumers and health professionals rely on for their safe and effective drugs.

On the next chart, in 2001, FDA conducted a limited survey of drugs compounded by 12 pharmacies. The drug products sampled included hormonal products, antibiotics, steroids and drugs to treat glaucoma, asthma, iron deficiency anemia, and erectile dysfunction. Ten of the 29 products we sampled failed one or more standard quality tests that we perform. Nine with failing analytical results failed potency testing, and some had less than 70 percent of their declared potency.

I want to emphasize that this was not a comprehensive scientific survey. It was a small sample size. But it does nonetheless demonstrate the seriousness of the problem.

By comparison, on the other side of the chart, each year FDA routinely samples and analyzes drug products made by commercial manufacturers. Since 1996, we have analyzed more than 3,000 samples of these products, and of these 3,000, only four failed potency tests.

Over the years, FDA has conducted enforcement activity against inappropriate pharmacy compounding, and my written testimony details some of our very recent enforcement cases.

We work cooperatively with our State partners, and I would like to give you an inside look at some of the problems that the State of Florida uncovered in a compounding pharmacy in the photos that are being shown there. Again, these photos are not representative of compounding pharmacies, but they are just to be illustrative examples of what can go wrong.

The first photo shows empty, uncapped vials used to compound respiratory therapy products. These vials are located in an uncovered box on the floor, and in bags on the upper shelves of a lavatory storage area.

The next photo shows an uncovered box of uncapped unit dose vials on the floor of a bathroom next to a toilet. The next photo shows an uncovered, unprotected flask of albuterol sulfate, a drug for asthma, located in the pharmacy's refrigerator next to some food. Again, we don't think these are representative, but they do clearly occur and the public health requires that we take steps to address them.

My written statement describes our statutory and regulatory authority over compounding. It covers the compounding provisions in section 127 of the FDA Modernization Act and the decision of the Western States versus Shalala case. Since that decision, FDA issued a compliance policy guide in May, 2002, that addresses how we will exercise our enforcement discretion under current law.

We respect the role of the States in matters that relate to pharmacy regulation. We also believe that there are areas where the Federal role is appropriate. These include maintaining a list of drugs that are inappropriate for compounding because they've been withdrawn from the market for safety reasons; two, overseeing the quality of bulk drug substances that are used in compounding; third, in conjunction with the States, investigating allegations of poor quality compounded drugs; and finally, determining when a pharmacy crosses the line between appropriate pharmacy compounding and manufacturing.

In closing, Mr. Chairman, I want to assure you that the agency's efforts to address pharmacy compounding issues are designed to balance the legitimate forms of pharmacy compounding with the need for Federal regulation when pharmacy compounding threatens to compromise public health.

I am happy to answer any questions, of course.

Senator BOND. Thank you very much, Dr. Galson.

[The prepared statement of Dr. Galson may be found in additional material.]

Senator BOND. We have been joined by Senator Roberts. I will call on him for any statements he wishes to make.

OPENING STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. I apologize to the witnesses and my colleagues for being late. I think they did a study around here at one time showing we're supposed to be at two places at the same time.

Senator Bond, I want to thank you for your leadership and for your sponsorship of this bill. I am glad to join you in holding this hearing on an important topic that has been simply brought to light over the last 2 years, and is gaining even more momentum. I think that most in the audience, and I know most in Washington, have been reading the Washington Post series this week on pharmaceutical safety, and that series of articles raises valid concerns with the safety of prescription drugs and that market and protecting patients. I think our committee can play a lead role in consumer protection. Again, I want to thank you for your leadership in this areas.

As has been said, today's hearing will focus on examining the overall practice of compounding pharmacies and where the industry is headed in really trying to address patient protection. I believe that Senator Bond and I have the same goal. We want to look at ways that those who enter the compounding pharmacy are entering into that profession are properly trained. We want to ensure that the proper checks are in place to protect patients, and we have looked at recent cases such as the Med 4-Home Pharmacy in Kansas City that have helped to illustrate the need for greater oversight.

The Med 4-Home did not follow proper recall and notification procedures for a batch of solutions that it had compounded. The product was an inhalant solution that was distributed nationwide and used to treat a variety of pulmonary disorders—and I'm talking about such things as asthma. Thousands of patients were contacted about the recall of these vials. I know that Kevin Kinkade of the Missouri State Board of Pharmacy is here with us today and he can speak about this event.

I fully recognize the benefits of compounding pharmacies. There's no question about that. They fill an important niche in the health care delivery system. However, many questions need to be answered. How do we define manufacturing versus compounding? What are we doing at the State level to enforce regulations currently on the books? How can we get States that do not have adequate regulation on the books to improve, and are those who are inspecting properly trained? Should we have a means test, or should we have a means to test products, once they have been compounded, to ensure they are safe and accurate doses? Are schools of pharmacy properly training individuals to compound, and what steps should they take to do so safely? Why is there not a system of adverse event reporting?

We have, and have had, two outstanding panels. I hope that they will be able to assist us in answering these questions. I'm sure they will.

In addition, Mr. Chairman, I have received comments from a compounding pharmacist, Dr. Steven Hotze of the Hotze Health and Wellness Center in Katy, TX. I have met with Dr. Hotze and he was eager to provide the committee with his input on this important topic. I would like to submit Dr. Hotze's testimony for the record at this point.

Senator BOND. Senator Roberts, without objection, it will be so admitted to the record.

[The prepared statement of Dr. Hotze may be found in additional material.]

Senator BOND. I have been advised that I am needed to make a quorum to vote on the chemical safety measure before the EPW Committee. I will ask Senator Ensign to ask five minutes of questions, and then Senator Roberts, if you would then ask questions, and should I be tied up, if you would continue with the introduction of witnesses.

Senator ROBERTS. I will be more than happy to do so.

Senator ENSIGN. Thank you, Mr. Chairman.

I normally don't take witnesses to task, Dr. Galson, but I do want to take you to task on something. You're a scientist, and to

present nonscientific data studies—and I'm glad you mentioned that it wasn't. But you have to remember, you're not talking to scientists up here. You can influence—you know, they look at you as an expert, and you presented that in a fashion that—you know, to Senators, they look at that as a study. That's irresponsible and you really shouldn't do that, especially as a representative of a governmental body.

We are trying to set public policy. You can create almost anything like that and call for a Federal Government regulation. I think of how often we see malpractice cases in States, and I could build an incredible case and use statistics like this and then say, yeah, we should have Federal licensing of physicians. But nobody is calling for that.

We have problems out there, and there are human beings and there are bad actors. There are mistakes that are made, and there will always be mistakes. There will always be bad actors no matter what the laws are.

What Senator Bond talked about, he was breaking the law. That's the bottom line. There were laws already being broken.

My question is—and Dr. Heinrich or you, whoever wants to take a stab at this—but one of the problems that we have here with pharmaceutical costs in this country is that we hear a lot from everybody throughout the medical field that the FDA is already overburdened and that the drugs take too long to get to market as it is. They are too expensive to get to market because of that, and they cost too much money to get to market because of that.

To now put an extra burden on the FDA, and let's say we decide to do this, could the FDA handle it, and do you have an idea about how much it would cost to handle that?

Ms. HEINRICH. Not related to the work that we did here on compounding, GAO recently did a review of the time it takes FDA to review new drugs. Actually, their review time has come down rather dramatically over the last, say, 5 years. But having said that, there is no question that it is costly to bring new drugs to market.

What you have here in drug compounding is something quite different, and that is——

Senator ENSIGN. I know what drug compounding is. My point is that the FDA already has difficulty doing its primary job function. Now adding something else on top, will this hurt your primary job function and do you have an estimate of the cost, of how much it would cost for it not to hurt your primary job function?

Ms. HEINRICH. In our discussions with FDA officials—and certainly Dr. Galson can speak for himself—but people did say that they are stretched now to cover their ongoing inspection requirements, and that to do more inspections in the area of compounding would be difficult.

Senator ENSIGN. Dr. Galson?

Dr. GALSON. Senator, I definitely appreciate your perspective, and as you said, I wasn't trying to present these as scientific data. Most notably, I wasn't trying to use them to urge or call for a new Federal regulation. It was merely to provide a few illustrative examples of what can happen.

We are stretched thin. We have extremely important public health responsibilities across the area—drugs, food, veterinarian drugs. So for us to embark on any new program in this area would require additional resources. But again, we're not calling for that and we haven't taken that position.

Senator ENSIGN. The only other comment I want to make on this—and I understand we may have some different viewpoints on this. But because of my experience in the medical fields, right now—I don't know if you remember, but we painted a great case up here for patient privacy, and then we got HIPPA. If you have heard of the implementation of HIPPA, we are hearing from health care professionals all over this country of how ridiculous some of this stuff has become.

That is my fear, that when we try to fix something, we make a lot more things worse. That happens time after time after time up here. There is a problem out there, and I freely admit that. There is a problem. But is the fix going to be worse than the problem? I guess that's the problem. HIPPA is a good example of where the fix is probably worse than the problem ever was. I just don't want us to end up with that.

Mr. Chairman, I appreciate your indulging me with this, but it is something that I have been pretty frustrated with, watching some of these things where we try to regulate medicine, which is a very inexact science, as we all know. Compounding will never be completely as precise as the machines and all of those types of things. You have human errors that can get involved in that. We have to be able to take that kind of stuff into account.

Thank you, Mr. Chairman.

Senator ROBERTS. [presiding]. I think the Senator has made an excellent point. I am extremely aware of the HIPPA regulations. When we had our first hearing in regards to the full committee on HIPPA, it was this Senator who waved the regulations around and indicated that I didn't think any Senator had really read all the regulations. I'm not sure if that's possible, in terms of a full understanding.

But I knew darned well that every hospital administrator in America had to read the regulations, had to hire people to read the regulations and interpret the regulations. Now we're into what is called the "law of unintended effects". So you make a good point.

It is important to pass legislation, but it is also extremely important to prevent bad legislation or counter-productive legislation from passing. I don't think Senator Bond or myself or anybody who wants questions answered—and I know the two witnesses want these questions answered as well—is proposing that the Federal Government impose a regulatory scheme that will pose problems for the FDA and any pharmacist throughout the country. So your caution is well taken and I thank you for the comment.

Senator Reed has joined us. I will yield to Senator Reed for any statement he would like to make and, for that matter, any questions he would like to raise at this point.

Senator REED. Thank you, Mr. Chairman. I have no opening statement so I will just get right to questions.

One area of concern is jurisdictional, between the State Boards of Pharmacy and the FDA. Apparently the FDA guidance is rather

amorphous. The FDA will let the State boards take "less significant" cases and they will take "more significant cases."

Dr. Galson and Dr. Heinrich, can you comment on that? Does it make sense that one approach to this issue is to try to clarify more specifically the breakdown of responsibility between the FDA and the local boards?

Dr. GALSON. We don't really think lack of clarity between the State and Federal Government in this particular area has been a problem. When we become aware of egregious cases or other specific issues, we work closely with the States to assist them, and when the States want our help about something they find out about on their own, there hasn't really been a problem in defining who has which role.

Senator REED. Do you have any ongoing technical assistance to the States in terms of this issue, where you are advising State Boards of Pharmacy on a regular basis about emerging issues of compounding abuses?

Dr. GALSON. We're in constant collaboration with them on compounding issues, as well as other outside groups.

Senator REED. Dr. Heinrich, do you have any comments?

Ms. HEINRICH. In our review, certainly we heard from pharmacists, pharmacy organizations, that they do believe there is a lack of clarity. Indeed, when FDA states that they do have overall authority under the Food, Drug and Cosmetic Act, that overlaps with State boards, there is ambiguity.

I think where we come out on this is that maybe we need to live with that because, with State resources being what they are, we may need to look to FDA even more in the future.

Senator REED. Thank you.

It is my understanding that pharmacists are not required to report adverse medical effects with compounded drugs, is that correct?

Dr. GALSON. That's correct.

Senator REED. Would it be helpful to have such a requirement in order to pinpoint more precisely the abuses before they become widespread?

Dr. GALSON. We haven't taken a position on that. Right now, with the traditionally manufactured drugs, the manufacturers have the legal responsibility to report those adverse events to us. As you know, there isn't really a system for the manufacturers to find out about the problems with drugs that they are compounding, and the compounders to find out about the adverse events related to the drugs that they're prescribing. But that is certainly something we could consider.

Senator REED. Dr. Heinrich?

Ms. HEINRICH. We might want to look at the experience of some States that, in fact, have required adverse event reporting. For example, in our review, we found that North Carolina does require adverse event reporting, and it would be good to look at their experience.

Senator REED. Very good.

I might have missed this in your statements, but is there any sort of trend in terms of compounding that should alarm us, or at

least make us more concerned? Is this going on with increased frequency or is it something that is happening at a steady rate?

Dr. GALSON. I don't think we have good data, because there isn't really comprehensive registration and monitoring of the system. We have seen a constant stream over the last few years of violations in other specific areas where we're concerned about public health, where we have taken action. But the trend data just isn't very good.

Senator REED. Thank you. Thank you both.

Thank you, Mr. Chairman.

Senator BOND. [presiding]. Thank you very much, Senator Reed.

Dr. Heinrich, in your written testimony you mentioned that the extent of drug compounding is unknown but appears to be increasing in the U.S. Can you give us an idea of the difficulties that GAO faced in attempting to capture the number of prescription drugs that are compounded in the U.S., as well as the number of adverse events?

Ms. HEINRICH. Yes. That was one of the issues that you really asked us to look into. We looked at information that we could glean from the Food and Drug Administration, trying to identify whether they could track the amount of bulk purchases of ingredients, and we found that that data system wasn't good, either, because you didn't have a common unit of analysis.

We went to pharmacy boards, we went to major compounders, the industry itself, and asked them if they could provide us that information, and nowhere could we get reliable data.

It is interesting that there are estimates that people have put out there. They say from one percent to ten percent of all prescription drugs are compounded, but when we really dug into that, there is really no basis for those estimates.

Senator BOND. Frankly, that's surprising, and disappointing.

In surveying the different States, I notice that you said Missouri and North Carolina have adverse event reporting systems, and in North Carolina, it has to really be adverse. I believe they only call "death" an adverse event. I think there are a lot of other things short of that that could be adverse.

Elsewhere, other than these two States, are there any other mandatory adverse reporting systems that you know of?

Ms. HEINRICH. Not that we were able to identify, but we could look into that further if you would like.

Senator BOND. Dr. Galson, don't you think that injuries and deaths from pharmacy compounding is a health issue that FDA needs to be more aggressive in addressing?

Dr. GALSON. We are very concerned about adverse events related to compounding. There is no question that that's one of the areas that concerns us the most. We spent a lot of money, upwards of $8 million per year, monitoring adverse events currently for traditionally manufactured drugs. That could be expanded. It is a cost issue.

Senator BOND. But right now, you get information anecdotally, really?

Dr. GALSON. That's right.

Senator BOND. Do you think the current system of State oversight of pharmaceutical compounding by State boards of pharmacy

is adequate and would meet the standards that FDA would establish?

Dr. GALSON. We think it's doing a reasonable job with us assisting the States, when that is necessary. As you know, there are different standards and different circumstances in each State.

We are working with the State boards of pharmacy and other organizations to create consensus type standards that would enable States to more carefully measure what's happening in their particular pharmacies against those standards, which will increase the compliance.

Senator BOND. I gather, in answer to the question from Senator Reed, you didn't think there's any problem with the lack of clarity with an uneven patchwork of the State-based and Federal system. Not only do I not see clarity, I don't see a system.

Dr. GALSON. I'm not saying there aren't, from time to time, problems. But lack of clarity hasn't stopped us from getting involved when we've seen a problem. That's really what I meant to convey.

Senator BOND. I guess as a first step in reporting adverse events, if we were to do something, would that be the logical first step, and are there any other steps that you could see—I mean, there are too many anecdotal reports of serious adverse events, death, fraud, simple errors, that mean that some patients who receive compounded pharmaceuticals are not getting what the doctor ordered, and maybe even dangerous bacteria and fungus.

What do we do about it? What role can we play so you and the States boards of pharmacy can do a better job?

Dr. GALSON. Certainly what we have mentioned about adverse events is one option, although we haven't taken a position on it. The Administration is continuing to work on developing a position on whether more legislative authority, regulatory authority, would be beneficial. We don't have a position to announce or to discuss with you right now.

We do think there is a lot of traction to be gained by the professional organizations and the other organizations working to develop standards, and then working with the States to make sure those standards are followed.

Senator BOND. Well, I would hope that this hearing is a wake up call to all of us, to know that the system is not working, and in many places I don't see a system. We want to involve all of the groups who will be represented here today, the associations, the government, the State boards.

But my urgent message to you and the administration is let's get with it, because Senator Roberts and I are getting to the age where we're going to need more compounded drugs. [Laughter.]

Seriously, there are many, many people who depend upon compounded drugs, who I know benefit in large measure by compounding. There is no question about that. We have got to keep the ability of small businesses, small pharmacies, to compound. It is vitally important.

But there has to be some reasonable assurance that, if somebody is making an error, or if there is a grossly inept situation like the Med 4-Home, or there's a criminal act like Dr. Courtney in Kansas City, somebody has got to catch them. And we're not going to depend upon a drug salesman saying, "By the way, I have done my

own research and found out that he isn't buying enough to develop the potency of drugs that he's been prescribing." That is not good enough.

Senator Roberts, do you have questions?

Senator ROBERTS. I have some questions for the GAO.

Registered pharmacies obviously vary greatly from State to State. In the States that you surveyed, what was the range of proportion of out-of-State pharmacies versus in-State? The reason that I'm asking that is there are three concerns:

Were there any differences in the registration requirements between in- and out-of-State pharmacies, and I think the answer to that is yes. How often did the experts you interviewed really believe that pharmacies should be inspected? And finally, considering there are such dramatic variations from State to State in their ability to inspect pharmacies due to a lack of inspectors and obviously the budget holes that our States find themselves in, is there a concern with the registration and certification process for registering out-of-State pharmacies? Out-of-State inspections don't seem to be very realistic.

Would you care to comment on that? I have probably strung together four questions, but feel free to answer all of them.

Ms. HEINRICH. As you said, there is great variability. It is difficult enough for many States to do the in-State inspections. It is much more difficult to monitor the out-of-State pharmacies, and oftentimes you get some of the international drugs there as well, to say nothing of what goes on with the Internet.

The States said consistently that oftentimes it's all they can do to follow up on complaints, that then they are unable to do the routine inspections. They would like to be able to do some every 2 years, every 4 years.

The other issue there is that the individuals who do the inspections may or may not have training that would help them provide oversight of compounding. I think only two of the States we looked at actually had pharmacists that were doing the inspections. The others were done by law enforcement. So that's an issue as well.

Senator ROBERTS. You mentioned the Internet pharmacy, which has become sort of a tidal wave in regards to consumers who are looking for cost-effective products—and I emphasize the cost.

Mr. Chairman, there has been a tidal wave, as you know, every 2 years, when we have these things called elections, you have candidates making trips and taking senior citizens to Mexico or Canada to purchase various products, and then coming back home and holding up the difference in cost.

And now, on the Internet, as evidenced by the Washington Post series—and I don't want to give them all the credit, but certainly they are doing a good job in that five-part series—you have a tidal wave here now of people ordering drugs over the Internet.

Do you have any comment about that in regards to what you have found, and how on Earth you could provide any reasonable inspection so that people are actually getting what they think they're getting? Feel free, Dr. Galson, to jump in here, if you would like.

Dr. GALSON. Right. We're extremely concerned about this. There is a flood of drugs coming into the country by various routes, including the Internet route, and there is really no system of assur-

ing the safety of those drugs. You don't know where they're coming from, even they are ordered from a website that has Canada in the name. You don't really know if they're coming from there or they have come from some Asian country where the quality isn't checked.

We have no way to intercept and monitor the packages. There are millions coming in. It's just impossible for each of these packages to be examined and looked at. So we are very concerned that this is escaping the really excellent system of maintaining the safety and efficacy of the U.S. drug supply.

Senator ROBERTS. I'm chairman of the Senate Select Committee on Intelligence, and also the subcommittee chairman on emerging threats. About four or 5 years ago I got interested in the food security challenge and danger. We now have that in the top ten of things that we're worried about.

It seems to me that any terrorist organization or, for that matter, any organized crime organization, could latch on to this and do great harm to the American public. I even identify this as a possible and probable area of concern in regards to the global war on terrorism. Now, maybe that is stretching it a little bit, but I don't really think so.

I think if you wanted to do great harm to a community or an area in the United States, particularly an area affected in regards to a senior population and the certain maladies that we all get as we're older, it is a cause of concern.

You stated in your testimony there were difficulties in interpreting some of the guidelines in the 2002 policy guidance. Do you intend on clarifying those provisions in the guidance, and when are you planning on updating that guidance?

Dr. GALSON. What we try to do is, when specific situations of interpretation come up, we do our best to clarify. At this moment, we believe this is as clear as we can be. Although we are continuing to think about improvements, we don't have a specific product or a date to point to when we're going to have further clarification or further details right now.

Senator ROBERTS. How do you define small versus large compounding?

Dr. GALSON. The major way we distinguish between acceptable and unacceptable compounding is if the compounding is being done for medical need, a legitimate medical need, where there is a relationship between the physician and the patient and the pharmacist. We consider that legitimate compounding.

When the compounding looks more like small or large scale manufacturing, that's when we become concerned, when large batches of product are made in advance of receipt of prescriptions. When copies of legitimate drugs are being prepared, when third parties are involved in reselling the drugs as well, we consider that large.

I just got a note here that we are working on a revised compliance policy guide based on public comments that are in our docket. I just don't have a time for when we're going to issue those.

Senator ROBERTS. I understand that.

How do you determine who to inspect and who not to?

Dr. GALSON. We inspect for cause, basically, when we hear about situations that raise concerns, or when information comes to us

from States or some other source of information that lets us know that there may be a problem, we do an inspection and work with the States.

Senator ROBERTS. What do you deem as acceptable or is an acceptable variance before a recall occurs?

Dr. GALSON. Numerically, you're asking?

Senator ROBERTS. Yes, sir. If you can pin that down, I know that's a——

Dr. GALSON. Yeah. I think I can't give you one number. We look at the product, we look at whether the product meets our criteria for quality, which are somewhat different, depending on the type of product—is it a pill, is it an inhalation, an injectable kind of drug. We make a call on that based on the public health risk involved with the product that we discover.

Senator ROBERTS. Mr. Chairman, I want to thank both witnesses for taking the time to come. I think this has been very educational. I have no further questions.

Senator BOND. Thank you very much to our witnesses. We will call the second panel.

Dr. Galson, if perhaps you could have you assistant turn that display panel around, so that those who are here may see the pictures that you took of the compounding pharmacy in Florida. Also, if you will allow the next witnesses to come forward, we thank you very much.

In the meantime, since several people have referred to newspaper articles on this, I am asking unanimous consent to include in the record a reprint of a three-part special report that appeared October 6–8, 2002, in the Kansas City Star, which has an excellent summary of this.

[The report referred to may be found in the Kansas City Star, October 6–8, 2002.]

Senator BOND. The second panel we would like to welcome and ask to come forward, please. Dr. Sarah Sellers, Executive Director of the Center for Pharmaceutical Safety a nonprofit public safety organization. She has a decade of experience as a pharmacist and she is completing a master of public health at Johns Hopkins, and serves on the FDA's advisory committee.

Daniel Herbert is president-elect of the American Pharmacists Association. A 1966 graduate of the Medical College of Virginia's School of Pharmacy, he owns three innovative community pharmacies in Richmond, VA which are involved in developing economical ways to deliver pharmaceutical care.

I am also pleased to welcome Kevin Kinkade from my home State of Missouri, a graduate of the State College of Pharmacy, a licensed pharmacist, and who has served as Executive Director of the Missouri State Board since 1984.

Also, very importantly, Dr. Bill Kennedy, a professional pharmacist registered in Florida and South Carolina, who for 20 years compounded pharmaceuticals in a retail pharmacy and national mail order respiratory pharmacy. He has invested millions of dollars in building a sterile, FDA-approved manufacturing facility.

So these witnesses will give us good, new perspectives on this situation. As I have indicated, you full statements will be made a part

of the record. We would ask you to try to summarize them in about five minutes.

I would call first on Dr. Sellers.

STATEMENTS OF SARAH L. SELLERS, PHARM.D, EXECUTIVE DIRECTOR, THE CENTER FOR PHARMACEUTICAL SAFETY; DANIEL A. HERBERT, RPh, PRESIDENT ELECT, AMERICAN PHARMACISTS ASSOCIATION; KEVIN KINKADE, EXECUTIVE DIRECTOR, MISSOURI BOARD OF PHARMACY; AND WILLIAM KENNEDY, OWNER, NEPHRON PHARMACEUTICALS CORPORATION

Mrs. SELLERS. Thank you. Mr. Chairman and members of the committee, thank you for the opportunity to speak with you today about the serious public health implications of pharmacy compounding. I am Sarah Sellers, a licensed pharmacist, with expertise in sterile compounding and public health. In 1998, I began serving on the FDA's Advisory Committee on Pharmacy Compounding.

It is unsettling that at a time when we are concerned about the quality of drugs accessed outside our borders because they may not meet our Federal regulatory standards, that we have a flourishing, unregulated drug industry within our own borders.

I began my career in a small, home care pharmacy that provided pharmacy compounded injections to patients for administration on their homes. When I asked permission to substitute the compounded drugs with FDA-approved products because of safety concerns, I was cautioned that it would be less profitable for the pharmacy. These compounded dosage forms did not undergo a validated sterilization procedure, were not tested for potency or purity, and the risks of using such a product were not identified, analyzed, or communicated to physicians or their patients.

This practice concerned me for both medical and ethical reasons. Patients were unknowingly exposed to drugs that did not meet strict Federal standards for safety and efficacy, manufacturing or labeling, to ensure safe use.

Based on my study of what is happening with pharmacy compounding, I believe there are four critical factors that need to be addressed. One, pharmacy compounded drugs do not meet our Federal safety requirements.

Two, as you heard from the GAO this morning, accurate, complete and unbiased information about the size and scope of the compounding industry in the United States is not available.

Three, current State compounding regulations are in some cases inadequate to protect public health and safety, and to prevent individual patient exposures to unacceptable risks.

Four, lack of oversight of the compounding industry has created new avenues to introduce commercial quantities of unapproved drugs into the marketplace through wholesale transactions.

Pharmacists are trained in pharmacy school to convert tablets to liquids and to make topical formulations to meet exceptional medical needs that cannot be met with approved products. But this practice, based on medical necessity, is very different from contemporary compounding. Contemporary compounding exploits current lapses in the law and resource constraints with regulators. This

has resulted in the emergence and growth of a substandard industry.

Because pharmacists are not required to detect or report problems associated with drugs they compound, the known cases of deaths, injuries, exposures and recalls of dangerous products are considered tip of the iceberg by public health experts.

Pharmacy compounded products have been associated with other injuries and deaths throughout the Nation. Last year, the CDC warned physicians and health systems to consider substandard compounded drug exposures in cases of unexplained infections following intraspinal injections, after an outbreak of fungal meningitis was associated with compounded products. CDC further warned that health systems may not even realize that they are purchasing compounded drugs.

In my opinion, the amendment to the Senate version of the Prescription Drug and Medicare Improvement bill, offered by Senators Bond and Roberts, to establish an FDA Advisory Committee on Compounding, is a critical first step, but it is only a first step. I believe new Federal legislation is necessary to protect patients and preserve the integrity of our current Federal system of drug regulation which is respected around the globe.

This legislation should consider the following:

One, there should be full disclosure to patients and prescribers when a prescription is filled with a compounded drug.

Two, compounding of drugs that are too difficult to make in a pharmacy setting should be prohibited and large-scale manufacturing of any drug product should be regulated by the FDA.

Three, there should be a strict paper trail for all chemicals used in compounding and reporting of any adverse events related to compounded products by pharmacists.

The basic assurances to public health and safety provided by the Federal Food, Drug and Cosmetic Act, that all citizens of this country rely on, should not be undermined. Unfortunately, I believe the unchecked growth and expansion of pharmacy compounding is threatening the Act's integrity.

I thank you for your time and would be pleased to answer any questions you may have.

Senator BOND. Thank you very much, Dr. Sellers.

[The prepared statement of Ms. Sellers may be found in additional material.]

Senator BOND. Now we will invite Mr. Herbert for his testimony

Mr. HERBERT. Good morning, Mr. Chairman.

Members of the committee, thank you for the opportunity to appear before you today and present the views of the American Pharmacists Association. I am Dan Herbert, a pharmacist, and president-elect. I have been in practice for 37 years and currently own three community pharmacies in Richmond, VA.

I have been involved in compounding throughout that entire career, and have been involved in a hospital setting, hospice, home infusion therapy, and community practice.

APhA represents the largest group of pharmacies in any association in the country who practice in virtually every practice setting. APhA supports the committee goal that patients receive safe and effective medication. As pharmacists, we rely upon quality as the

first step in our work to help patients get the most of their medication therapy. When providing a quality product involves tailoring a medication for an individual patient, we use our scientific training and education to compound the medication to meet the patient's needs.

My goal today is to share with you my experience with pharmacy compounding, the value it can bring when performed for the right reasons and in the right way. I compound 10 to 20 times per day in my practice, and while it is challenging to quantify the actual number of APhA members who regularly compound, I think it is safe to say that virtually every pharmacist is involved in compounding at some point in their career, and many on a daily basis.

The committee has so eloquently stated many of our positions in your opening statements that I am going to skip over the justification of why we need to preserve compounding. You have already acknowledged that it is a vital patient care service and that keeping it available to the public is an important thing to do.

We fully recognize the need for pharmacy compounding to conform to high professional standards. The question that you have already asked and that plagues the profession and our regulators, the State boards of pharmacy, is how to distinguish between what I do, compounding, and manufacturing. It has been a difficult distinction to implement because of the complexity and range of legitimate compounding activities. The key element in making any such distinction is the existence of a pharmacist-prescriber-patient relationship.

Furthermore, compounded drugs are not for resale but, rather, are personal and responsive to a patient's immediate needs. My compounding practice is for those patients that I serve every day, and their physicians.

APhA is undertaking several activities to advance and improve pharmacist compounding, such as publishing resources for pharmacists to improve the practice. Also, I am chairing an APhA committee setting strategic directions for the profession, including proposing steps for advancing compounding quality.

One aspect of our committee's work to date is the preliminary categorization of compounding to distinguish between the types of compounding a pharmacist can provide based on his basic pharmacy education and that type of compounding that may require additional specialized training, and perhaps even certification or accreditation. Because compounding encompasses a broad scope of activities, this categorization is important in focusing quality improvement efforts and resources.

Finally, in collaboration with the National Association of Boards of Pharmacy and the United States Pharmacopeia, APhA has recommended exploring the value of voluntary programs to improve compounding activity in certain categories. Improving our efforts to provide quality compounded products will require collaborative efforts of consumers, the profession, the boards of pharmacy, and the FDA. Each stakeholder has an expertise that is essential in assuring the continued availability of this practice with the quality patients deserve.

The profession must take the lead in guiding the regulatory agencies on how to draw the line between compounding and manufacturing, and in developing guidelines to make those standards real in everyday practice. The State boards of pharmacy should maintain their primary regulatory role of pharmacy practice, including compounding, and will likely be tasked with new initiatives to enhance the current regulatory efforts. Pharmacists and APhA are ready to partner with stakeholders to develop effective strategies to continue to improve the quality of compounding practices.

Thank you for the opportunity

Senator BOND. Thank you very much, Mr. Herbert. We certainly look forward to working with you when we have the results of your recommendations.

[The prepared statement of Mr. Herbert may be found in additional material.]

Senator BOND. Now I turn to Mr. Kinkade and find out what is going on in Missouri since we last talked. Welcome.

Mr. KINKADE. Good morning.

Mr. Chairman, members of the committee, thank you for the invitation to speak here today on a matter that is very important to consumers and regulators, as well as the medical and pharmacy professions.

While not all pharmacies practice the art of compounding, those that do provide a time-honored and valued service to their patients. Just as in the past, there are situations today where only compounded drug products can fulfill the need that some patients have for effective drug therapies.

As technology and science increase our ability to manufacture new drugs, so do these same elements have an impact on the practice of compounding. This places new and complex challenges before State boards of pharmacy, who are charged with the protection of public health and safety on a State level.

A number of cases around the Nation have brought national attention to the practice of compounding. The Robert Courtney case in Kansas City, which was an example of outrageous and demoralized conduct, certainly brings to light what great harm to others a single criminal can do. Other cases of incompetent acts or actions that resulted in errors that have harmed or even caused the death of patients have also garnered attention. Our primary concern must always be for the health and safety of our citizens who receive health care, and concerning today's subject, compounded products.

My written testimony outlines in more detail the major changes and regulations and processes that have been made in Missouri in order to maintain adequate minimum standards of practice in pharmacies that compound.

We have also reviewed our inspection process in all areas in order to ensure that our field staff of the board of pharmacy are functioning with the latest knowledge base possible.

Whether or not the issue is criminal fraud against consumers, or it is a matter of incompetent or negligent practices, we must be in a position to act quickly and effectively. Resources for the proper inspection of pharmacies, as well as the ability to respond timely to consumer complaints through the use of investigations, must be

the first priority. Additionally, appropriate quality assurance practices, both in pharmacies that practice compounding as well as with the boards of pharmacy that regulate them, must be included as well.

As an example, the Missouri Board of Pharmacy has chosen to test samples of compounded drugs from State-licensed pharmacies on a random, unannounced basis. Once a sample is obtained, it will be tested using certified laboratory procedures that will also include full chain of custody controls for each item tested. Pharmacies will be reimbursed for their cost for whatever samples that are selected.

All States have in place a voluntary compliance program that utilizes State inspectors to review standards of practice in pharmacies. Missouri utilizes this approach, when possible, to seek any corrective actions that may be necessary within a particular practice setting. However, when necessary, in Missouri we use discipline power as well as authority to seek relief in State courts to halt unsafe practices through restraining orders and permanent injunctions.

Legislation was introduced this last year that would have provided additional authorities to the Board. Some of these included embargo authority, the provision of a specific class of license for pharmacies that compound, and to allow expedited procedures against licensees that the Board believes are practicing pharmacy in an unsafe manner. The bill that was introduced in both the House and the Senate did not pass due to some differences between the State association and the Board. If we are successful in the next legislative session, such authorities will further enhance our ability to act effectively when situations warrant such use of those powers.

Finally, Federal agencies such as the FDA can work with various States and the National Association of Boards of Pharmacy to develop national definitions and guidelines to maintain an appropriate balance between State and Federal regulatory responsibilities. An improved definition of compounding versus manufacturing on the Federal level would help define the role of State and Federal agencies as well.

The Missouri Board of Pharmacy again wishes to thank the committee for this opportunity to testify, and is certainly available to work with Congress and Federal agencies on improving oversight over compounding practices.

Thank you.

Senator BOND. Mr. Kinkade, obviously I'm very proud of the way that Missouri has responded. We had a horrible tragedy, and several others, and I hope other States can learn a positive lesson without having to go through the very real problems that were caused in our State. The response, given the State of knowledge, seems to be outstanding and perhaps a model, and we welcome comments on it. But I want to commend you and the State Board for being very, very aggressive and we look forward to seeing how the system continues to work in Missouri.

[The prepared statement of Mr. Kinkade may be found in additional material.]

Senator BOND. With that, let me turn now to the testimony from Mr. Kennedy. Thank you so much for being here and for sharing your experience on both the compounding and manufacturing side.

Mr. KENNEDY. Thank you.

Mr. Chairman and members of the committee, thank you sincerely for your efforts to shed public light on the phenomenon in the country today of pharmacists boldly compounding massive quantities of prescription drugs. I believe that I am uniquely qualified to speak to you on this topic.

I am both a licensed pharmacist who was involved in a large-scale compounding, and I am now the owner of an FDA-approved manufacturing facility in Orlando, FL. We produce sterile product, oral inhalation solutions, so most of my comments are going to be toward the inhalation market. The drug albuterol has already been mentioned, and the term Med 4-Home has been mentioned earlier about Missouri, so a lot of my comments are related to oral inhalation.

Since we have been an FDA-approved plant, we have been able to win a contract from the Veterans Administration, the VA contract, which is one of the largest contracts in the country for being able to provide albuterol and ipratropium. We were selected by the Government and we won it on quality and we won it on price, to be able to provide all of the albuterol and ipratropium that is manufactured that VA hospitals and patients at home use in their nebulizers.

The public is at risk, an alarming great risk, and you are to be commended for your interest in and pursuit of non-FDA compliant compounding.

At this time I would like to point out that I agree fully with what other pharmacists are saying, what Mr. Herbert said, as the president of the American Pharmacists Association. If that model is followed, I don't think we have that great a problem. I think the problem becomes all of a sudden when you have the independent pharmacy who is compounding items and doing a great job for the community—like if you go to your local pharmacists in any town in America and get a product compounded, whether it be a veterinarian who has written a prescription, or your general practice doctor, or your dentist, in which your prescription needs to be altered so that your medication is more usable for you, every American citizen deserves that.

My contention and my problem is when we try to do something like this as a pharmacist and try to do it on a large, massive scale, and compound or manufacture whatever the FDA wants to call it, millions of doses per month. For example, Med 4-Home as was mentioned earlier. So I think the problems come in when you try to do it on a massive scale and you're not a manufacturer.

You have large companies, you have public companies, you have large private companies that are hiding behind the auspices of a compounding pharmacy that should be considered manufacturing due to the scale of product and number of prescriptions they are producing on a monthly basis.

I would like to give you my history and background and show sort of my relationship that I have had with the FDA.

In 1972, I purchased my own retail drug store, Thayer's Colonial Pharmacy, Inc., located in Orlando, FL. This drug store had been in Orlando for many years, with a reputation for finding unique prescription drugs and compounding various discontinued formulations. Included in this were many combinations of two or more drugs. It could be dermatology products, it could be respiratory products, it could be gastric products, it could be changing formulations for pediatrics so that they wouldn't have adverse side effects.

But in the mid-1880s at Thayer's, we began compounding various respiratory medications on a broader scale. This business grew rapidly, including a large portion of mail order transactions. We attracted much attention from the industry because of the size we grew to in a short period of time.

Around 1990, the FDA paid us a visit. Their mission was to investigate my compounding pharmacy. After 2 weeks of intense scrutiny, they determined that I should be labeled a manufacturer and ordered that I cease and desist this compounding division of Thayer's, the part in which we were doing massive respiratory drugs, not the part of doing dermatological preparations or individual compounds where you have the physician-patient-pharmacist relationship that Mr. Herbert spoke of.

The FDA representative said, "If you want to be in the manufacturing business, then you must have an FDA-approved manufacturing facility." Of course, the back room of my drug store did not qualify, okay? We're talking 1990, and today we're talking, of course, 2003.

In 1991, following the FDA's instruction, I set out to secure the approvals and financing necessary to open a proper manufacturing facility. Although I was a bit naive at the outset, I soon learned that I was involved in a daunting process. In my case, it took over 6 years, 6 years, to secure approval for my first generic drug product, which is an ANDA, Abbreviated New Drug Application, in my plant. It was arduous, capital intensive, and certainly the most challenging endeavor of my career in health care. However, I now understood the rules and knew this was necessary to begin providing prescription drugs on a large scale to the public.

How did I know this? I knew this because the FDA had told me so.

In 1997, Nephron Pharmaceuticals was up and running as an FDA-approved and registered facility. Our focus is oral inhalation solutions to treat asthma, bronchitis, and Chronic Obstructive Pulmonary Disease. And by the way, COPD is the fourth leading cause of death in this country today, and is fast becoming the third leading cause of death. So this is a big field, oral inhalation solutions, for these patients. As you can see in my written testimony, I have six different ANDAs.

Now, by national pharmaceutical standards, Nephron is a little guy. We are very small. Even so, I just want to show you what it entails to manufacture drugs as a small manufacturer.

Our 76,000 square foot facility is designated for full FDA compliance. Our production room design houses controlled environment rooms, based on the 1997 ISPE sterile manufacturing facilities guidelines and was developed with the help of FDA.

I also have some exhibits in my package which show you the different parts of our plant, the sterility part, the water system, and what we have to go through.

Senator BOND. Mr. Kennedy, those will all be accepted in the record. We very much appreciate that.

Mr. KENNEDY. Thank you.

One other thing I would like to quickly mention is that in this facility, just to show you the number of people that it requires to be FDA approved for a small plant the size of a gnat, compared to a large company.

In our regulatory department we have four people that are responsible for nothing but FDA compliance and reporting. We have a quality assurance department that consists of 41 people that do nothing but handle document control for the FDA—validation, batch records. We have nine degreed chemists that work in our lab, and they have technicians. We have 19 degreed microbiologists and technicians who continually monitor the environment of the plant. We have 117 production personnel, and we have specialists that do blow, fill and seal, which is the type of technology we use to manufacture. These personnel operate at the facility in compliance with the regulations.

Now, just to talk about some of the standards, called standard operating procedures.

Senator BOND. Mr. Kennedy, we have a time deadline, and actually you have answered and I will take that off my questioning time. But you have answered the questions about the costs. We are very interested in that. But if you could wrap it up and submit as much of your testimony as possible, we would appreciate it.

Mr. KENNEDY. OK.

Perhaps to attack this problem, the FDA instituted a rule that all oral inhalation drugs have to be sterile. That was in May of 2002. There still seems to be some discussion within the FDA and the industry where this applies to compounding pharmacy or not for oral inhalation.

However, in my trips around the country marketing my products, I encounter time after time non-FDA approved companies that are actually compounding millions and millions of doses of these products per month.

Thank you.

Senator BOND. Thank you very much, Mr. Kennedy.

[The prepared statement of Mr. Kennedy may be found in additional material.]

Senator BOND. Let me go back to Mr. Kinkade. As I indicated, you are apparently the first State to institute random testing. What do you think the merits are, what is the status of implementation, what are the problems of this? This was one of the first things that we discussed, I think, when I met with you and representatives of pharmacies and prescribing physicians. How does the system work and what is the status of implementation?

Mr. KINKADE. Well, the status at this point is that we are receiving bids in from various laboratories that will be contracted with to do the actual testing of the drugs. Missouri requires that on this type of system, or to expend this much money out of State budgets, you are required to have a bidding process. So that is a fairly time-

consuming process that we are about to conclude, and we expect to start testing next month.

Along with that, of course, I might want to add here that not only will the Board be doing its random testing, but our new standards, our new regulations will require pharmacies to do their own testing of certain lots of products that they produce and have those results on hand.

The testing that the Board will do primarily was in the area of how samples would be collected. There are various ways to do that, depending on whether the product has a shelf life or whether it is the type of product that is compounded and then used or administered immediately. There will be methods to be able to take material in both of those cases, as well as situations where we may receive public complaints and actually, in a few cases, have to go or use undercover operations in order to take a random test. But we are setting up procedures for all of those types of scenarios that we find exist in the marketplace, with the type of compounds that are being made.

I also emphasize here that we are not just talking about sterile products, although that is our primary concern, because in addition to potency issues are products that we will be testing for, with sterile products, we will also be testing for such things as sterility and pyrogenicity in these products, to make sure that they do, in fact, meet the claims and standards that they are supposed to when compounded.

Senator BOND. Thank you very much, Mr. Kinkade. We obviously would be interested to learn how the system works when it gets implemented.

Let me go back to Dr. Sellers. You mentioned loopholes that the contemporary pharmacy compounders are taking advantage of. You gave us four very good ideas for legislation. Are there any other things that you see need to be addressed?

Mrs. SELLERS. I think it's very important that both physicians and patients are apprised of the risks that may be associated with compounded drugs. Typically, physicians outsource the information on the risks associated with compounded drugs to pharmacists, and if there is not a requirement for the pharmacist to disclose those risks, it becomes very difficult to make an autonomous decision about a prescription medication that is in the best interest of a patient. So I think there needs to be a balanced reporting of both benefits and risks for these products.

Senator BOND. Let me ask one question. I assume we're all going along with this, but if you have any comments on it, let me ask for your comments.

No. 1, does anybody think we should not have a mandatory Federal system of reporting adverse events? Anyone? Mr. Herbert.

Mr. HERBERT. APhA would support voluntary reporting.

Senator BOND. Voluntary, not mandatory.

Mr. HERBERT. Voluntary, nonpunative.

Senator BOND. Would you support mandatory reporting at the State level?

Mr. HERBERT. I think so. I'm not sure what we're talking about. The nature of compounding itself is such that we don't often have the information to report any adverse effects. I'm not sure you

would get anything. Mandating you to report something that you would hardly ever know about, you would always be reporting something after the fact. As you are describing, you would be reporting deaths, and they seldom happen. But I'm not sure what the value of that reporting is. So you are creating a bureaucracy that reports something that I'm not sure does anything.

Mrs. SELLERS. I would also like to comment, that before you can report a problem, you need to detect the problem. If we are not looking for problems with the medications that we are making, we are not going to be able to report them.

Senator BOND. A good point.

Any comments, Mr. Kinkade, Mr. Kennedy?

Mr. KINKADE. I would make the comment that, at least from our standards that we have in Missouri now, we have included requirements not only for recalls, when necessary, but the type of information that is required and who is to be contacted on the type and seriousness of the recall.

One of the things we learned in the Med 4-Home case was that that particular facility had received some complaints from patients that we weren't aware of. So one of the new standards that we have implemented in Missouri is that all compounding pharmacies maintain files so that inspectors can review those files on any complaints that patients would provide a licensee on a compounded product.

In addition to that, any adverse reactions, again recalls on infection rates on any types of compounded products, do have to be reported to the Board now.

Senator BOND. One other item. I thought I heard agreement that if a pharmacy is making quantities of compounded drugs—not compounding for the individual prescription written by a doctor for a specific patient—should this be an FDA regulated manufacturing pharmacy? Mr. Kennedy, I think that was your point.

Mr. Herbert?

Mr. HERBERT. I would say quantity, in and of itself, is not the best indicator, but the existence of a relationship that you are filling the order pursuant to a physician's order for a specific person—but you could do that for many patients. So it's not just the quantity; it is the relationship.

Senator BOND. Is it a specific doctor prescribing for a patient or patients. If one doctor has 20 patients that need a compounded drug——

Mr. HERBERT. Exactly.

Senator BOND. —then that pharmacist is compounding for those patients.

Mr. HERBERT. Exactly. So the quantity alone is not the indicator. It is the relationship that exists, and are you doing it to meet a medical need. It is not just creating it to put on the shelf and go out and market the stuff.

Senator BOND. Any other comments on that?

Mr. KINKADE. Just briefly, we have run into some pharmacies who, perhaps due to a shortage of a manufactured drug on the market, have attempted to sell compounded products on a wholesale basis—in other words, outside the prescription/patient/prescriber relationship. In those cases, it is certainly our interpreta-

tion that we feel the Federal law is clear, that that is manufacturing and not the practice of pharmacy.

Senator BOND. Sounds reasonable to me.

At this point I am going to turn the rest of the hearing over to Senator Roberts, because I have a commitment that I have to keep. I thank all of our witnesses today. It has been very helpful.

I am asking unanimous consent that we will include in the record the statement of the American Society of Health-System Pharmacists, and testimony from the International Academy of Compounding Pharmacists.

[The statements of the American Society of Health-System Pharmacists and the International Academy of Compounding Pharmacists may be found in additional material.]

Senator BOND. We will keep the record open for a week for further comments. I think we have raised some questions, and maybe we have some misunderstandings, so if you wish to submit something to clarify those, we would appreciate your doing it within a week. We may have some additional questions, and other members of the committee may have some questions. We would appreciate if you would try to respond to those promptly.

Finally, as we are all looking at what we should introduce on the Federal level, whether we should introduce it on a Federal level, we would appreciate receiving your advice by January 15th on whether you think the time is ripe for some kind of reporting, if some kind of regulation is necessary. If you would report to us by that time, we would very much welcome your input.

Again, our sincere thanks for enlightening us. It is a complicated subject, and obviously, I have got to learn more. But I thank you for your guidance.

I will turn the gavel over to Senator Roberts.

Senator ROBERTS. [presiding]. Thank you, Mr. Chairman. Again, I want to thank you for your leadership. I am very happy to cosponsor our amendment.

I might say at the outset that when we meet with the Finance Committee staff as of this next week to try to work out the amendment as part of the overall bill, that the first step is what Dr. Sellers indicated, i.e., at least an advisory board.

We gave a lot of leeway to the Secretary to make sure that all groups are represented, and if we get this right, we are talking about the National Association of Boards of Pharmacy, the pharmacy groups, the physician groups, the hospital groups, the consumer and patient advocate groups, law enforcement agencies, which are very important, victims of unsafe or diluted compound drugs or their families, and those that would be determined appropriate by the Secretary. So we haven't really defined the universe yet, but we want to make sure that it is comprehensive and that all groups and all advice and counsel would be considered in the advisory process.

I'm going to ask Mr. Kennedy a question because it gets to the Hobson's choice or the Catch-22, or what Senator Ensign was talking about, in an effort to try to bring some degree of control and safety to this whole issue.

You went through 6 years, six long years with the FDA, and as you have indicated in your statement, you have, in order to comply

with the FDA, to maintain your business, which now has FDA approval, of course, four people responsible for all FDA compliance, 41 people in regards to document control—that sounds like "Dr. K" over in Iraq—quality control, nine degreed chemists, 19 degreed microbiologists, 117 production personnel, four blow, fill, seal specialists—I don't know what that means, but I will take it for granted that they are necessary—and 22 production equipment assistance and "one partridge in an FDA regulatory tree." [Laughter.]

Mr. KENNEDY. Correct.

Senator ROBERTS. Dr. Sellers, you have given excellent testimony, and you have had an experience associated with your home care pharmacy in compounding experience. You are the duty expert here on the panel in regards to this universe that we really haven't got our arms around.

How on Earth can we make progress without getting into a regulatory nightmare and having a manufacturer having to go through 6 years of a gauntlet in regards to FDA? I'm not trying to pick on the FDA. They have their requirements as well. But that seems to me to be a real problem area.

Mrs. SELLERS. Yes, sir. There are other countries that have dealt with this issue by creating small manufacturers licenses to produce drugs that are not commercially manufactured. That may be one option to explore as a potential solution. There may be State licensed facilities that may be able to fill this role as well.

I think we should incentivize small businesses that can meet those needs and do it in a manner that produces uniform quality products that are needed by specific patient populations.

Senator ROBERTS. This 6 years business and all of this employment, all that's involved is the cost driver, that basically is one of the causes that we have a problem with. It is going to be a real challenge for us.

Talking to Dr. Sellers, what actions did you take after wrestling with the medical and ethical issues associated with your home care pharmacy compounding experience, and what was the outcome of your course of action?

Mrs. SELLERS. I initially contacted the State Board of Pharmacy in Florida, and they took no action one compounding in the State of Florida. I left that practice and went to other practices in my community and found the same type of compounding existed in those pharmacies as well. That is when I decided to start studying the issue more fully and began efforts to gain more education in public health.

Senator ROBERTS. Well, you actually answered my next question. You stated you quickly learned that your compounding experience was not unique. How did you learn this, and you have already addressed that. And then what action did you take upon learning this, and your action was your current capacity.

What do you believe are the loopholes, the major loopholes, in regards to the contemporary pharmacy compounders, that they're really taking advantage of?

Mrs. SELLERS. I think there is overlapping regulatory authority which creates a situation where there is a questionable role in State and Federal regulation that can be exploited. I have seen where there have been difficulties when the FDA has attempted to

go in and regulate a pharmacy that the FDA believes is actually manufacturing, and they have been denied entry into pharmacies, denied access to inspect, because the pharmacy has stated that they are regulated by the State. So perhaps it's a better way to State that the overlapping authorities and the unclear mandates between the Federal and State Governments creates a situation where it is very difficult to have effective oversight.

The infrastructure for oversight is further complicated by the fact that pharmacies are not registered with the FDA, so, in fact, the FDA may not know where mass manufacturing is going on or where unsafe practices exist. On the State level, because we have limited resources and so few inspectors who may not be trained to look for public health problems, we may not be identifying problems.

Senator ROBERTS. Mr. Herbert, that leads me to the question I wanted to ask you. What can we do to work with the schools of pharmacy to improve their curriculum, and then, obviously, you get into a better training situation?

Mr. HERBERT. To work with the schools of pharmacy?

Senator ROBERTS. Yes, sir.

Mr. HERBERT. I'm not sure I can answer that. The schools of pharmacy, for the most part, are not teaching compounding these days. It is not part of the curriculum in many schools of pharmacy in the country. Whether you have the ability to require that is something I can't answer.

Having standards for what the practice is about may back in that process. If you have to meet standards when you're practicing, then you would have to learn them somewhere, and that may precipitate the reinstitution of training programs in schools of pharmacy. But, frankly, it is not part of the curriculum in most of them today.

Senator ROBERTS. It occurs to me that I should have asked you, basically, do you feel that the schools of pharmacy are providing adequate training for pharmacy compounding, and the answer to that is probably no.

Mr. HERBERT. The answer to that is no.

Senator ROBERTS. Some pharmacy technicians are allowed to compound. Do you feel they have the proper training to compound, and I would guess the answer to that is no.

Mr. HERBERT. I don't know that I would agree with that. I think they can be trained to properly compound.

Senator ROBERTS. Obviously, I think they should be required to have some minimum requirements in terms of training and education.

What is your opinion about States licensing or, at the minimum, registering a pharmacy technician?

Mr. HERBERT. Registering a pharmacy technician?

Senator ROBERTS. Yes, sir.

Mr. HERBERT. I think it should be done.

Senator ROBERTS. All right.

Mr. HERBERT. It is done in our State.

Senator ROBERTS. That concludes the questions I had. I want to associate myself with the remarks of the distinguished chairman,

and would ask if any member of the panel would like to add anything at this point before we conclude the hearing.

Mr. KENNEDY. Yes, sir, I would like to add one point.

With the present enforcement of the FDA in compounding, and as I talk about the quantity and size of the compounding, of the commercialization of the compounding going on, I don't understand why, even with the regulations and rules that are on the books today for the FDA, why there cannot be more of a determination of whether a company is a manufacturer or a compounder. I think they have the ability to do that, but for some reason, I think that is being overlooked.

Senator ROBERTS. That doubtlessly should be a priority issue for the advisory board, if we can get that first step done.

Thank you for taking the time out of a very busy schedule to come and testify on a growing national health concern.

This hearing is concluded.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF JANET HEINRICH, GAO

PRESCRIPTION DRUGS

State and Federal Oversight of Drug Compounding by Pharmacies

Why GAO Did This Study

Drug compounding—the process of mixing, combining, or altering ingredients—is an important part of the practice of pharmacy because there is a need for medications tailored to individual patient needs. Several recent compounding cases that resulted in serious illness and deaths have raised concern about oversight to ensure the safety and quality of compounded drugs. These concerns have raised questions about what States—which regulate the practice of pharmacy—and the Food and Drug Administration (FDA) are doing to oversee drug compounding. GAO was asked to examine (1) the actions taken or proposed by States and national pharmacy organizations that may affect State oversight of drug compounding, and (2) Federal authority and enforcement power regarding compounded drugs.

This testimony is based on discussions with the National Association of Boards of Pharmacy (NABP) and a GAO review of four States: Missouri, North Carolina, Vermont, and Wyoming. GAO also interviewed and reviewed documents from pharmacist organizations, FDA, and others involved in the practice of pharmacy or drug compounding.

What GAO Found

A number of efforts have been taken or are under way both at the State level and among pharmacy organizations at the national level that may strengthen State oversight of drug compounding. Actions among the four States reviewed included adopting new regulations about compounding and conducting more extensive testing of compounded drugs. For example, the pharmacy board in Missouri is starting a program of random testing of compounded drugs for safety, quality, and potency. At the national level, industry organizations are working on standards for compounded drugs that could be adopted by the States in their laws and regulations, thereby potentially helping to ensure that pharmacies consistently produce safe, high-quality compounded drugs. While these actions may help improve oversight, the ability of States to oversee and ensure the quality and safety of compounded drugs may be affected by State-specific factors such as the resources available for inspections and enforcement.

FDA maintains that drug compounding activities are generally subject to FDA oversight, including its authority to oversee the safety and quality of new drugs. In practice, however, the Agency generally relies on States to regulate the limited compounding of drugs as part of the traditional practice of pharmacy. In 1997, the Congress passed a law exempting drug compounders that met certain criteria from key provisions of the Federal Food Drug and Cosmetic Act (FDCA), including the requirements for the approval of new drugs. These exemptions, however, were nullified in 2002 when the U.S. Supreme Court ruled part of the 1997 law to be an unconstitutional restriction on commercial speech, which resulted in the entire compounding section being declared invalid. Following the court decision in 2002, FDA issued guidance to indicate when it would consider taking enforcement actions regarding drug compounding. For example, it said the Agency would defer to States regarding "less significant" violations of the Act, but would consider taking action in situations more analogous to drug manufacturing.

Mr. Chairman and Members of the Committee: I am pleased to be here today as you consider State and Federal oversight to ensure the safety and quality of compounded prescription drugs. Drug compounding—the process of mixing, combining, or altering ingredients to create a customized medication for an individual patient—is an important part of the practice of pharmacy. Common examples of compounded drugs include tailor-made medications for patients who are allergic to an ingredient in a manufactured drug. Drug compounding is part of pharmacy education and, like other aspects of pharmacy practice, it is regulated by State pharmacy practice acts, which in turn are enforced by State boards of pharmacy. All 50 States describe drug compounding in their State laws and regulations on pharmacy practice, although specific statutes or regulations vary across States. At the Federal level, the Food and Drug Administration (FDA), which oversees the introduction of new drugs into

the marketplace under the Federal Food, Drug and Cosmetic Act (FDCA),[1] maintains that compounded drugs are generally subject to the act.

While drug compounding is an important part of ensuring that medications are available to meet individual patient needs, the quality and extent of drug compounding have surfaced as important issues in recent years. For example, several compounding cases in the past several years have resulted in serious illnesses and deaths, raising concern about oversight to ensure the safety and quality of compounded drugs. In addition, concerns have been raised by FDA and others that some pharmacies are going beyond traditional drug compounding for individual patients by, for example, compounding and selling large quantities of drugs without meeting safety and other requirements for new manufactured drugs. Because both States and the Federal Government have oversight responsibilities, you asked us to address (1) the actions taken or proposed by States and national pharmacy organizations that may affect State oversight of drug compounding, and (2) Federal authority and enforcement power regarding compounded drugs.

My testimony today is based in part on discussions with the National Association of Boards of Pharmacy (NABP), as well as a review we conducted of four States: Missouri, North Carolina, Vermont, and Wyoming. We selected these States based on their geographic location and variation in compounding regulations. Two of the States came to our attention as having taken unique steps with regard to oversight of compounded drugs, and the other two had each adopted new regulations on drug compounding. For each of the four States, we reviewed State statutes and regulations, interviewed officials from the State board of pharmacy, and reviewed relevant documents such as pharmacy inspection forms. In addition to examining State-level actions, we examined national industry efforts by interviewing officials from the American Pharmacists Association, the International Academy of Compounding Pharmacists, the American Society of Health-System Pharmacists, the National Association of Chain Drug Stores, and Professional Compounding Centers of America, which provides training to pharmacists and also sells bulk ingredients for drug compounding. We also contacted and obtained information from the United States Pharmacopeia (USP), which is a nonprofit agency that develops standards for pharmaceuticals. Finally, to examine Federal authority and enforcement power, we reviewed Federal statutes, FDA compliance policy guides, court decisions, and other relevant documents, and interviewed FDA officials and industry experts. We conducted our work from August 2003 to October 2003 in accordance with generally accepted government auditing standards.

In summary, efforts at the State level and among pharmacy organizations at the national level have been taken or are under way to potentially strengthen State oversight of drug compounding. Actions among the four States we reviewed included adopting new statutes and regulations about compounding, such as requirements for facilities and equipment, and conducting more extensive testing of compounded drugs. For example, the pharmacy board in Missouri is starting a program of random testing of compounded drugs for safety, quality, and potency. At the national level, industry organizations are working on standards for compounded drugs that could be adopted by the States in their laws and regulations, thereby helping to ensure that pharmacies consistently produce safe, high-quality compounded drugs. While these actions may help improve oversight, the ability of States to oversee and ensure the quality and safety of compounded drugs may be affected by State-specific factors such as the resources available for inspections and enforcement. For example, in three of the four States we reviewed, pharmacy board officials indicated that resource limitations affected their ability to conduct routine inspections.

FDA maintains that drug compounding activities are generally subject to its oversight, including its authority to oversee the safety and quality of new drugs. In practice, however, the Agency generally relies on States to regulate the compounding of drugs as part of the traditional practice of pharmacy. In 1997, the Congress passed a law exempting drug compounders that met certain criteria from key FDCA provisions, including safety and efficacy requirements for the approval of new drugs. However, the entire section of the law dealing with drug compounding was nullified in 2002 after the U.S. Supreme Court ruled that part of it was an unconstitutional restriction on commercial speech. Following the court decision in 2002, FDA issued guidance to indicate when the Agency would consider taking enforcement actions regarding drug compounding. For example, it said the Agency would generally defer to the States for "less significant" violations of the FDCA but would consider taking action in situations more analogous to drug manufacturing.

[1] *See* 21 U.S.C. § 355.

BACKGROUND

For most people and many pharmacies, filling a prescription is a matter of dispensing a commercially available drug product that has been manufactured in its final ready-to-use form. This has been particularly true in the U.S. since the rise of pharmaceutical manufacturing companies. In addition to meeting Federal safety and efficacy requirements before a new drug is marketed, the drugs manufactured by these companies are routinely tested by FDA after marketing. According to FDA, the testing failure rate for more than 3,000 manufactured drug products sampled and analyzed by FDA since fiscal year 1996 was less than 2 percent. Drug manufacturers are also required to report adverse events associated with their drugs, such as illness and death, to FDA within specified time frames.

Drug compounding, which has always been a part of the traditional practice of pharmacy, involves the mixing, combining, or altering of ingredients to create a customized medication for an individual patient. According to the American Pharmacists Association, some of the most commonly compounded products include lotions, ointments, creams, gels, suppositories, and intravenously administered fluids and medication. Some of these compounded drugs, such as intravenously administered chemotherapy drugs, are sterile products that require special safeguards to prevent injury or death to patients receiving them. For example, sterile compounding requires cleaner facilities than nonsterile compounding, as well as specific training for pharmacy personnel and testing of the compounded drug for sterility.

The extent of drug compounding is unknown, but it appears to be increasing in the U.S. While industry representatives, the media, and others have cited estimates for the proportion of prescription drugs that are compounded ranging from 1 percent to 10 percent of all prescriptions, we found no data supporting most estimates.[2] FDA does not routinely collect data on the quantity of prescriptions filled by compounded drugs. Similarly, we found no publicly available data, either from FDA or from industry organizations, on the amount of bulk active ingredients and other chemicals that are used in drug compounding in the U.S. However, many State officials, pharmacist association representatives, and other experts we interviewed reported that the number of compounded prescriptions, which had decreased when pharmaceutical manufacturing grew in the 1950s and 1960s, has been increasing over the past decade.

Problems have come to light regarding compounded drugs, some of which resulted in death or serious injury, because the drugs were contaminated or had incorrect amounts of the active ingredient. Unlike drug manufacturers, who are required to report adverse events associated with the drugs they produce, FDA does not require pharmacies to report adverse events associated with compounded drugs. Based on voluntary reporting, media reports, and other sources, FDA has become aware of over 200 adverse events involving 71 compounded products since about 1990. These incidents, including 3 deaths and 13 hospitalizations following injection of a compounded drug that was contaminated with bacteria in 2001, have heightened concern about compounded drugs' safety and quality. In addition, a limited survey conducted by FDA's Division of Prescription Drug Compliance and Surveillance in 2001 found that nearly one-third of the 29 sampled compounded drugs were subpotent—that is, they had less of the active ingredients than indicated.

FDA and others have also expressed concern about the potential for harm to the public health when drugs are manufactured and distributed in commercial amounts without FDA's prior approval. While FDA has stated that traditional drug compounding on a small scale in response to individual prescriptions is beneficial, FDA officials have voiced concern that some establishments with retail pharmacy licenses might be manufacturing new drugs under the guise of drug compounding in order to avoid FDCA requirements.

ACTIONS TAKEN OR UNDER WAY BY STATES AND NATIONAL ORGANIZATIONS TO STRENGTHEN STATE OVERSIGHT OF DRUG COMPOUNDING, BUT AFFECT LIKELY TO VARY FROM STATE TO STATE

We found efforts at the State level and among national pharmacy organizations to potentially strengthen State oversight of drug compounding. Actions among the

[2] A 2001 draft report of a study contracted by FDA included an estimate that about 6 percent of all prescriptions were compounded but cautioned that there was considerable uncertainty around this estimate due to limited data. The report acknowledged that definitive statistics on compounding activities were not available. Eastern Research Group Inc., *Profile of the Pharmaceutical Compounding Industry*, draft final report prepared for the Food and Drug Administration, August 27, 2001.

four States we reviewed included adopting new drug compounding regulations and random testing of compounded drugs. At the national level, industry organizations are working on standards for compounded drugs that could be adopted by States in their laws and regulations. According to experts we interviewed, uniform standards for compounded drugs could help ensure that pharmacists across States consistently produce safe, quality products. While these actions may help improve oversight, the ability of States to oversee and ensure the quality and safety of compounded drugs may be affected by their available resources and their ability to adopt new standards and enforce penalties.

FOUR STATES REVIEWED HAVE TAKEN A VARIETY OF APPROACHES TO STRENGTHEN OVERSIGHT

The four States we reviewed have taken a variety of approaches to strengthen State oversight.

• *Missouri*. The pharmacy board in Missouri has taken a different approach from other States: it is in the process of implementing random batch testing of compounded drugs. No other State has random testing, according to an NABP official. Random testing will include both sterile and nonsterile compounded drugs and the board plans on testing compounded drugs for safety, quality, and potency. A Missouri pharmacy board official said testing will include random samples of compounded drugs in stock in pharmacies in anticipation of regular prescriptions, random selection of prescriptions that were just prepared, and testing of compounded drugs obtained by undercover investigators posing as patients. The official added that random testing will help to ensure the safety and quality of compounded drugs and is also intended to serve as a deterrent for anyone who might consider purposely tampering with compounded prescriptions.

• *North Carolina*. North Carolina is the only State in the country that requires mandatory adverse event reporting involving prescription drugs, including compounded drugs, according to an NAPB official. Regulations in North Carolina require pharmacy managers to report information to the pharmacy board that suggests a probability that prescription drugs caused or contributed to the death of a patient. This reporting system, which does not extend to incidents of illness or injury, allows the board to investigate all prescription-drug-related deaths and determine whether an investigation is warranted.

• *Vermont*. The pharmacy board in Vermont overhauled the State's pharmacy rules in August 2003 to address changes in pharmacy practice, including the increase in Internet and mail-order pharmacies, according to the pharmacy board chairman. For example, the chairman reported that prior to the adoption of the new rules, Vermont had no definition of out-of-state pharmacies and no requirements for these pharmacies to have a Vermont license to do business in the State. The board chairman said that the new rule requiring licensing for out-of-state pharmacies would provide a mechanism to monitor pharmacies that ship prescription drugs, including compounded drugs, into the State. In addition, he added that the board revised the rules for compounding sterile drugs by including specifics on facilities, equipment, and quality assurance measures.

• *Wyoming*. Prior to March 2003, Wyoming did not have State laws or rules that established specific guidelines for drug compounding, aside from a definition of drug compounding, according to a pharmacy board official. The new rules include requirements for facilities, equipment, labeling, and record keeping for compounded drugs, as well as a specific section on compounding sterile drugs. In addition, under the new rules, the official added that pharmacy technicians-in-training are no longer allowed to prepare compounded drugs, including sterile products, which is a more complex procedure requiring special equipment to ensure patient safety.

EFFORTS OF NATIONAL ORGANIZATIONS MAY HELP STATES STRENGTHEN OVERSIGHT OF DRUG COMPOUNDING

At the national level, industry organizations are working on uniform practices and guidelines for compounded drugs and a committee of national association representatives recently began work on developing a program that would include certification and accreditation for drug compounding that could be used for State oversight. Groups such as the NABP concluded that State oversight of drug compounding would be strengthened if the States had uniform standards and other tools that could be adopted to address the quality and safety of compounded drugs. Several experts that we spoke with said national standards for compounding drugs that could be incorporated into State laws and regulations could help to ensure the quality and safety of compounded drugs. One expert noted that an advantage to incorporating compliance with national compounding standards into State laws is that

it would be easier for States to keep up with updated standards without going through the process of legislative changes.

NABP developed and updated a Model State Pharmacy Act that provides standards for States regarding pharmacy practice. Recently revised in 2003, the model act includes a definition of drug compounding and a section on good drug compounding practices. According to the executive director of NABP, many States have incorporated portions of the model act into their State pharmacy statutes or regulations by including similar definitions of drug compounding and components of NABP's good drug compounding practices. For example, officials in Missouri and Wyoming reported using the model act's good drug compounding practices as a guideline for developing their drug compounding regulations. In addition, USP has established standards and guidelines for compounding nonsterile and sterile drug products, both of which are being updated by expert committees. An official told us that these revisions would be completed early in 2004.

In addition, recognizing that there is no coordinated national program to oversee compounding practices and that States' oversight may vary, NABP recently began working with other national organizations, including the American Pharmacists Association and USP, to create a steering committee to develop a national program to provide a national quality improvement system for compounding pharmacies and the practice of compounding. The committee, which held its second meeting in October 2003, is developing a program that is anticipated to include (1) the accreditation of compounding pharmacies, (2) certification of compounding pharmacists, and (3) requirements for compounded products to meet industry standards for quality medications. To strengthen State oversight of drug compounding, these accreditations, certifications, and product standards, once developed, could be adopted by the States and incorporated into their requirements for compounding pharmacists and pharmacies.

FACTORS SUCH AS AVAILABLE RESOURCES MAY AFFECT STATES' ABILITY TO OVERSEE COMPOUNDED DRUGS

Although there are several efforts by States and national organizations that may help strengthen State oversight, some States may lack the resources to provide the necessary oversight. State pharmacy board officials in three of the four States reported that resources were limited for inspections, for example:

- The Missouri pharmacy board director reported that pharmacy inspections typically occur every 12 to 18 months; however, an increase in complaints has resulted in less frequent routine pharmacy inspections, because investigating complaints takes priority over routine inspections.
- North Carolina has six inspectors for about 2,000 pharmacies, which the State pharmacy board director said are inspected at least every 18 months. The director added that it is difficult to keep up with this schedule of routine inspections with the available resources while also investigating complaints, which take first priority.
- In Vermont, the pharmacy board chairman reported that, for a period of about 8 years until January 2003, pharmacy inspectors were only able to respond to complaints and not conduct routine inspections because of a shortage of inspectors. Vermont now has four full-time inspectors that cover the State's 120 pharmacies; however, in addition to routine pharmacy inspections, the inspectors are also responsible for inspecting other facilities such as nursing homes and funeral homes. The chairman added that the board would like to have pharmacies inspected annually but it is difficult to keep up with the current schedule of inspections once every 2 years.

Since drug compounding may occur in mail-order and Internet pharmacies, the compounding pharmacy may be located in a State different from the location of the patient or prescribing health professional. Three of the four States we reviewed had a large number of out-of-state pharmacies that were licensed to conduct business in those States, and inspection and enforcement activities may differ for these pharmacies. For example, Wyoming has 274 licensed out-of-state pharmacies, which is nearly twice as many as the number of in-state licensed pharmacies. The four States we reviewed said that they have authority to inspect out-of-state pharmacies licensed in their states but because of limited resources, they generally leave inspections to the State in which the pharmacy is located. Regarding enforcement authority, all four States reported having authority to take disciplinary action against out-of-state pharmacies licensed in their States.

While the pharmacy boards in all four States we reviewed can suspend or revoke pharmacy licenses or issue letters of censure, enforcement mechanisms vary. For example, Missouri and North Carolina are not authorized to charge fines for violations; however, Wyoming can fine a pharmacist up to $2,000 and Vermont can fine a pharmacy or pharmacist $1,000 for each violation. Further, not all State phar-

macy boards have the authority to take enforcement action independently. For example, in Missouri when attempting to deny, revoke, or suspend a license through an expedited procedure, the pharmacy board must first file a complaint with an administrative hearing commission. Only after the commission determines that the grounds for discipline exist may the board take disciplinary action.

Pharmacy board officials reported relatively few complaints and disciplinary actions involving drug compounding. For example, of the 307 complaints received and reviewed by the board of pharmacy against pharmacies and pharmacists in Missouri in fiscal year 2002, only 5 were related to drug compounding.[3]

FDA ASSERTS OVERSIGHT AUTHORITY UNDER FDCA BUT GENERALLY RELIES ON STATES TO REGULATE DRUG COMPOUNDING

FDA maintains that drug compounding activities are generally subject to FDA oversight, including the "new drug" requirements and other provisions of the FDCA. In practice, however, the Agency generally relies on the States to regulate the traditional practice of pharmacy, including the limited compounding of drugs for the particular needs of individual patients. In recent years, the Congress has attempted to clarify the extent of Federal authority and enforcement power regarding drug compounding. In 1997, the Congress passed a law that exempted drug compounders from key portions of the FDCA if they met certain criteria. Their efforts, however, were nullified when the Supreme Court struck down a portion of the law's drug compounding section as an unconstitutional restriction on commercial speech, which resulted in the entire compounding section being declared invalid.[4] In response, FDA issued a compliance policy guide to provide the compounding industry with an explanation of its enforcement policy, which included a list of factors the Agency would consider before taking enforcement actions against drug compounders.

FDA ASSERTS JURISDICTION TO REGULATE DRUG COMPOUNDING UNDER FDCA

FDA maintains that FDCA requirements, such as those regarding the safety and efficacy requirements for the approval of new drugs, are generally applicable to pharmacies, including those that compound drugs. The Agency recognized in its brief submitted in the 2002 Supreme Court case that applying FDCA's new drug approval requirements to drugs compounded on a small scale is unrealistic—that is, it would not be economically feasible to require drug compounding pharmacies to undergo the testing required for the new drug approval process for drugs compounded to meet the unique needs of individual patients. The Agency has stated that its primary concern is where drug compounding is being conducted on a scale tantamount to manufacturing in an effort to circumvent FDCA's new drug approval requirements. FDA officials reported that the Agency has generally left regulation of traditional pharmacy practice to the States, while enforcing the act primarily when pharmacies engage in drug compounding activities that FDA determines to be more analogous to drug manufacturing.

FDA MODERNIZATION ACT EXEMPTED DRUG COMPOUNDERS FROM SOME FDCA REQUIREMENTS BUT WAS DECLARED INVALID

Federal regulatory authority over drug compounding attracted congressional interest in the 1990s, as some in the Congress believed that "clarification is necessary to address current concerns and uncertainty about the Food and Drug Administration's regulatory authority over pharmacy compounding."[5] The Congress addressed this and other issues when it passed the FDA Modernization Act of 1997 (FDAMA), which included a section exempting drugs compounded on a customized basis for an individual patient from key portions of FDCA that were otherwise applicable to manufacturers.[6] According to the congressional conferees, its purpose was to ensure continued availability of compounded drug products while limiting the scope of compounding so as "to prevent manufacturing under the guise of compounding."[7]

In order to be entitled to the exemption, drug compounders had to meet several requirements, including one that prohibited them from advertising or promoting

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[3] The State pharmacy board officials that we spoke with reported that most complaints and disciplinary actions cover dispensing errors related to manufactured drugs, such as incorrectly counting the number of pills for a prescription.

[4] *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

[5] S. Rep. No. 105-43, at 67 (1997).

[6] These portions covered "adequate directions for use" labeling, manufacturing, and new drug approval requirements. *See* former 21 U.S.C. § 353a(a). Pub. L. No. 105-115, 111 Stat. 2296, former section 503A.

[7] H.R. Conf. Rep. No. 105-399, at 94 (1997).

"the compounding of any particular drug, class of drug, or type of drug."[8] This prohibition was challenged in court by a number of compounding pharmacies and eventually resulted in a 2002 Supreme Court decision holding that it was unconstitutional. As a result, the entire drug compounding section was declared invalid.[9] However, the Court did not address the extent of FDA's authority to regulate drug compounding.

CURRENT FDA ENFORCEMENT FOCUSES ON DRUG COMPOUNDING OUTSIDE OF THE TRADITIONAL PRACTICE OF PHARMACY

FDA issued a compliance policy guide in May 2002, following the Supreme Court decision, to offer guidance about when it would consider exercising its enforcement authority regarding pharmacy compounding.[10] In the guide, FDA stated that the traditional practice of drug compounding by pharmacies is not the subject of the guidance. The guide further stated that FDA will generally defer to State authorities in dealing with "less significant" violations of FDCA, and expects to work cooperatively with the States in coordinating investigations, referrals, and follow-up actions. However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of FDCA, the guide stated that FDA has determined that it should seriously consider enforcement action and listed factors, such as compounding drug products that are commercially available or using "commercial scale manufacturing or testing equipment," that will be considered in deciding whether to take action.[11]

Some representatives of pharmacist associations and others have expressed concern that FDA's compliance policy guide has created confusion regarding when FDA enforcement authority will be used. For example, some pharmacy associations assert that FDA's guidance lacks a clear description of the circumstances under which the Agency will take action against pharmacies. In particular, they pointed to terms in the guide, such as "very limited quantities" and "commercial scale manufacturing or testing equipment" that are not clearly defined, and noted that FDA reserved the right to consider other factors in addition to those in the guide without giving further clarification. FDA officials told us that the guide allows the Agency to have the flexibility to respond to a wide variety of situations where the public health and safety are issues, and that they plan to revisit the guide after reviewing the comments the Agency received, but did not have a time frame for issuing revised guidance.

In several reported court cases involving FDA's regulation of drug compounders, the courts have generally sided with FDA. Two cases we identified involved drug compounders engaged in practices that were determined to be more analogous to drug manufacturing. In a district court case decided this year, the court upheld FDA's authority to inspect a pharmacy specializing in compounding, noting that it believed that FDA's revised compliance policy guide was a reasonable interpretation of the statutory scheme established by FDCA.[12]

CONCLUDING OBSERVATIONS

While drug compounding is important and useful for patient care, problems that have occurred raise legitimate concerns about the quality and safety of compounded drugs and the oversight of pharmacies that compound them. However, the extent of problems related to compounding is unknown. FDA maintains that drug compounding activities are generally subject to FDA oversight under its authority to oversee the safety and quality of new drugs, but the Agency generally relies on

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[8] *See* former 21 U.S.C. § 353a(c).

[9] Both the district and appellate courts held that the prohibition was unconstitutional. However, the district court held that the prohibition was "severable" and that the rest of the pharmacy compounding section remained good law. While the appellate court agreed with the district court on the constitutional question, it disagreed on the severability issue and invalidated the entire section. The Supreme Court agreed with both courts on the constitutional issue, but because the severability decision was not challenged, the Court did not rule on it, and left it in place. *See Thompson v. Western, States Medical Center*, 69 F. Supp. 2d 1288 (D. Nev. 1999), aff'd in part and rev'd in part, 238 F. 3d 1090 (9th Cir. 2001), aff'd, 535 U.S. 357.

[10] This guide was similar to an earlier compliance policy guide published by FDA in 1992. After the drug compounding section of FDAMA was declared invalid, FDA determined that it needed to issue new guidance to the compounding industry on what factors the Agency would consider in exercising its enforcement discretion regarding drug compounding.

[11] "Compliance Policy Guide: Compliance Policy Guidance for FDA Staff and Industry", Chapter 4, Sub Chapter 460, May 2002.

[12] *In the Matter of Establishment Inspection of Wedgewood Village Pharmacy, Inc.*, 270 F. Supp. 525, 549 (D. N.J. 2003).

States to provide the necessary oversight. At the State level, our review provides some indication that at least some States are taking steps to strengthen State oversight, and national pharmacy organizations are developing standards that might help strengthen oversight if the States adopted and enforced them. However, the effectiveness of these measures is unknown, and factors such as the availability of resources may also affect the extent of State oversight.

Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or other Members of the Committee may have at this time.

Contact and Acknowledgments

For further information, please contact Janet Heinrich at (202) 512–7119. Individuals making key contributions to this testimony included Matt Byer,Lisa A. Lusk, and Kim Yamane.

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PREPARED STATEMENT OF STEVEN K. GALSON, M.D., M.P.H.

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Steve Galson, the Deputy Director of the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency). I am also the Acting Director of the Center while Dr. Janet Woodcock is on detail to the Office of the Commissioner.

I appreciate the opportunity to discuss FDA's role with regard to pharmacy compounding. In my testimony, I will discuss the Agency's activities and strategies for addressing public health issues associated with pharmacy compounding. I will touch on our current statutory and regulatory authority, how the Agency has exercised that authority, and our future plans in this area.

BACKGROUND

By most estimates, pharmacy compounding is a growing business. Many compounding pharmacies have established Internet websites to promote and sell

their products. The Agency's strategies for addressing pharmacy compounding have had to evolve to respond to the public health challenges associated with this growing area while at the same time preserving the benefits that pharmacy compounding offers in meeting a public health need.

FDA views traditional pharmacy compounding as the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription.[1] In its simplest form, it may involve taking an approved drug substance and making a new formulation to meet the medical needs of a specific patient. For example, it may involve formulating the product without a dye or preservative in response to a patient allergy. Or it might involve making a suspension or suppository dosage form for a child or elderly patient who has difficulty swallowing a tablet or a capsule. These traditional forms of pharmacy compounding are an important component of our pharmaceutical armamentarium. Although these products technically may be considered unapproved new drugs because they differ from the approved formulation of the drug, FDA has exercised enforcement discretion to allow these legitimate forms of pharmacy compounding, which are regulated under State laws governing the practice of pharmacy.

We believe that the vast majority of pharmacies engaging in pharmacy compounding provide a valuable medical service that is an integral part of our modern health care system. However, we have become aware of instances involving compounding in which the risks of obtaining a product of substandard quality may outweigh the benefits of obtaining the compounded drug. In addition, we have seen abuses, such as large-scale drug manufacturing under the guise of pharmacy compounding.

In recent years, we have witnessed some compounding pharmacies creatively marketing new compounded products that they assert are "better" than available therapies. We are not aware of data supporting these claims. Sometimes these pharmacies compound a product containing a form of an active ingredient that has not been approved by FDA, such as 4-aminopyridine, an experimental drug compounded for patients with multiple sclerosis. In other instances, drugs are compounded even though FDA has removed them from the market after determining that they were unsafe. We also have seen drugs compounded that are essentially copies of commercially available products.

Compounding pharmacies then sell these copies for less than the approved commercially available product. These appear to be compounded for economic reasons rather than genuine medical need. In such cases, we believe the consumer would be better served by the commercially available drug, which has been determined to be safe and effective and manufactured under rigorous good manufacturing practice requirements.

Although there is limited hard data on the actual amount of pharmacy compounding that is occurring in this country, pharmacy compounding appears to be a big and growing business. In April 2001, we commissioned a study on the compounding industry by the Eastern Research Group, Inc. According to their August 2001 report, over 650 pharmacies fill more than 13 million prescriptions for compounded products per year.

Although many more pharmacies compound (some estimates put the number at more than 3,000 compounding pharmacies) this relatively small number of pharmacies that specialize in compounding appear to account for a majority of the drugs compounded nationally. Some estimate that compounding represents one percent of all of the prescriptions filled each year. In 2003, according to one estimate, this would amount to 30 million prescriptions for compounded products. In some cases, these prescriptions may be compounded in pharmacies that dispense only compounded medications or in other pharmacies for which compounding is a large percentage of their business.

Pharmacy compounding, by definition, involves making a new drug whose safety and efficacy have not been demonstrated with the kind of data that FDA ordinarily would require in reviewing a new drug application.[2] Although most pharmacists are well-trained and well-equipped to safely compound certain medications, not all pharmacists have the same level of skills and equipment, and some products that are

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[1] Under the compounding-related provisions of the Food and Drug Administration Modernization Act, pharmacy compounding was not defined to include mixing or reconstituting commercial products in accordance with the manufacturer's instructions or the product's approved labeling. Reconstituting means the return, usually by adding liquid, of a drug previously altered for preservation and storage to its original state for administration to a patient. This type of manipulation, when done in accordance with approved labeling, should not adversely affect the safety or efficacy of the drug. (The provisions were struck down by the Supreme Court on April 29, 2002.)

[2] In some cases, it may simply involve taking an approved drug and making a new formulation.

compounded may be inappropriate for compounding. In some cases, we have reason to be concerned about the quality of the drugs being compounded and the potential risks to patients who may take them. In some instances, compounders may lack sufficient controls (equipment, training, testing, or facilities) to ensure product quality or to compound difficult products such as sterile or modified release drugs. If compounding is done on a large scale and is not done properly, compounders can expose large numbers of patients to health risks associated with unsafe or ineffective medications. This may be of particular concern if patients are taking an ineffective compounded product in lieu of a proven therapy. In addition, compounding large quantities of drugs and copying commercially available approved products in compounding pharmacies circumvents important public health requirements and undermines the drug approval process—the evidence-based system of drug review that consumers and health professionals rely on for safe and effective drugs.

Recent Enforcement Activity

The following examples of recent FDA enforcement actions against compounding pharmacies illustrate some of these concerns:

Fentanyl "Lollipops": In August 2002, during in a joint FDA/New Hampshire inspection, FDA determined that a pharmacy was compounding Fentanyl "Lollipops" and dispensing them without the labeling and other packaging and patient safety features required by FDA for the approved product. Fentanyl is a narcotic analgesic that could pose a safety hazard to children if distributed without appropriate safety measures. FDA issued a "warning letter" to the firm and the firm agreed to cease distribution of this product.

Methylprednisolone Acetate: In September 2002, a compounding pharmacy in South Carolina recalled all lots of its methylprednisolone acetate products based on reports of four patients who developed a rare fungal infection after taking the drug. Ultimately, a total of six patients were infected, and one died. A joint FDA/South Carolina inspection revealed that the firm did not have adequate controls over its compounding operations to ensure the necessary sterility. When the firm refused to voluntarily recall other injectable products or to provide FDA with a complete list of all products distributed, FDA issued a nationwide alert on all injectable drugs prepared by the firm. FDA is aware of several other cases of contamination and adverse events associated with compounded sterile injectable products.

Large Volume Interstate Shipments: In September 2002, FDA issued a "warning letter" to a California pharmacy after it determined during a joint FDA/California inspection that the firm was not operating as a retail pharmacy. The firm was using commercial scale manufacturing equipment and making large quantities of drugs for shipment across California and to patients in other States. In March of 2002, the firm issued a recall of compounded inhalation solutions due to microbial contamination.

In each of these cases, as is the case in most pharmacy compounding actions, FDA has proceeded jointly with the State in which the pharmacy is located. In many of the cases, however, questions have arisen concerning FDA's authority over the compounding activities. In some cases, FDA had difficulty obtaining access to the compounding pharmacy to determine whether the firm was engaging in dangerous practices. The pharmacies argued that they were not subject to FDA regulation because they were compounding pharmacies. FDA had to get a warrant to obtain access to the facilities and records of compounding activities. One of these incidents is discussed in more detail below.

Wedgewood Village Pharmacy: On July 7, 2003, a U.S. Magistrate Judge in the U.S. District Court of New Jersey denied Wedgewood Pharmacy's motion to quash FDA's warrant for administrative inspection of the pharmacy. The warrant application was filed after the U.S. Drug Enforcement Agency's (DEA) requested assistance from FDA in conducting an on-site inspection of Wedgewood.

The Magistrate Judge held, in part, that (1) FDA had authority to apply for a warrant to inspect the pharmacy; (2) it is not FDA's burden to prove that the entity it seeks to inspect is not entitled to the pharmacy-related exemptions from FD&C Act; and (3) the Compliance Policy Guide stating that FDA would not attempt to regulate traditional pharmacy compounding practices was a reasonable interpretation of the FD&C Act. The pharmacy owner appealed to the District Court Judge the magistrate's order denying the motion to quash the administrative inspection warrant. The District Court held a hearing on October 16, 2003. A ruling in this case is pending.

Because FDA was not permitted to complete its inspection in this case and several others, the Agency has been delayed, from obtaining the evidence needed to assess whether drug manufacturing is occurring under the guise of compounding or if compounding practices that raise public health concerns are present.

STATUTORY AND REGULATORY AUTHORITY

Although compounding was widespread when the FD&C Act was first enacted in 1938, there were no provisions specifically dedicated to compounding, as distinguished from manufacturing of drugs. After the 1962 amendments to the Act expanded the universe of drugs that require FDA pre-market approval to include drugs that are not already generally recognized by experts as effective, courts have interpreted expansively the Act's provisions to require pre-market approval of virtually all prescription drugs. It is widely recognized, however, that compounded drugs could not meet the approval requirements, in part because they traditionally are made in small amounts for individual patients according to a prescription. In addition, it is usually not feasible to study them in clinical trials to establish their safety and efficacy or prepare new drug applications for all of the different types of compounded products that might be prescribed.

Several of the Act's provisions that pertain to drugs generally include compounded drugs. The specific statutory provisions that may apply to compounded drugs are: (1) the definition of "drug" (section 201 (g) of the Act); (2) the misbranding and adequate directions for use requirements for drugs (section 502 of the Act); (3) the adulteration and current good manufacturing practice (cGMP) requirements for drugs (section 501(a)(2)(B) of the Act); and (4) the new drug approval provisions (section 505 of the Act). Literal application of these statutory drug authorities could mean that, technically, virtually all compounded drugs violate the Act, despite the long history of allowing certain types of compounding and the important public health benefits provided by such compounding of medically necessary drugs that are not otherwise available. Until the 1997 provision discussed below, Congress had not explicitly exempted compounded drugs from the preceding requirements of the Act.

Today, the Act does specifically address compounding in two specific provisions; the registration provisions and the inspection provisions. In each case, it provides an exemption that is narrowly tied to the specific requirements of those two provisions. Under the requirements for drug registration, although compounding is specifically included among the activities that would require an establishment to register with FDA (section 510(c) of the Act), an exemption is provided for pharmacies that, among other conditions, do not compound for sale "other than in the regular course of their business of dispensing or selling drugs . . . at retail" (section 510(g)(1) of the Act). The same language limits the types of records that FDA may review during an inspection of a pharmacy (section 704 of the Act).

Because these exemptions do not extend to other statutory requirements, such as pre-approval requirements that would significantly restrict compounding, FDA has historically exercised its enforcement discretion in a manner that defers to the States, as the regulators of the practice of pharmacy, to serve as the primary regulators of the practice of pharmacy compounding. FDA's focus in recent years has been on drug manufacturing that operates under the guise of pharmacy compounding. FDA also has worked cooperatively with the National Association of Boards of Pharmacy (NABP) and the U.S. Pharmacopeial Convention (USP) to address good compounding practices, and with the States on a case-by-case basis to address instances of compounding that raise public health and safety issues.

Compliance Policy Guide of 1992

In March 1992, FDA issued a compliance policy guide (CPG), to delineate the Agency's enforcement policy on pharmacy compounding. This CPG relied on the exercise of enforcement discretion rather than legal exemptions from new drug and other statutory requirements. The pharmacy community expressed concerns about how FDA intended to exercise its enforcement discretion and sought legislation to clarify the boundaries of FDA's authority over pharmacy compounding. In 1997, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA) to specifically address FDA's role in the regulation of pharmacy compounding.

Food and Drug Administration Modernization Act of 1997

On November 21, 1997, the President signed FDAMA (P.L. 105-115). Section 127 of FDAMA added sections 503A to the FD&C Act, to clarify the status of pharmacy compounding under Federal Law. Under section 503A, 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 requirement, or cGMP); (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. Section 503A of the Act took effect on November 21, 1998, 1 year after FDAMA was signed into law.

Thompson v. Western States Medical Center

In November 1998, the solicitation and advertising provisions of section 503A were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. The U.S. District Court for the District of Nevada ruled in the plaintiffs' favor. FDA appealed to the U.S. Court of Appeals for the Ninth Circuit. On February 6, 2001, the Court of Appeals declared section 503A to be invalid in its entirety (Western States Medical Center v. Shalala, 238 F.3rd 1090 (9th Cir. 2001)). The government petitioned for a writ of certiorari to the U.S. Supreme Court for review of the Ninth Circuit's decision that the solicitation and advertising provisions of section 503A were unconstitutional restrictions on commercial speech. The Supreme Court granted the writ and issued its decision in the case on April 29, 2002.

The Supreme Court affirmed the Ninth Circuit's decision that section 503A of the FD&C Act was invalid in its entirety because it contained unconstitutional restrictions on commercial speech (i.e., prohibitions on soliciting prescriptions for and advertising specific compounded drugs). The Court did not rule on, and therefore left in place, the Ninth Circuit's holding that the unconstitutional restrictions on commercial speech could not be severed from the rest of section 503A. Accordingly, all of section 503A is now invalid.

Compliance Policy Guide of May 2002

Once the statutorily created exemptions from the new drug, misbranding and adequate directions for use requirements were deemed invalid for compounded drugs, FDA determined that it needed to issue guidance to the compounding industry on what factors the Agency would consider in exercising its enforcement discretion in this area under current law. In May 2002, FDA issued a *Guidance for Industry—Pharmacy Compounding—Compliance Policy Guide*, which is based on the CPG of March 1992.

The guidance states that FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional compounding activity is not the subject of the guidance.

However, when the scope and nature of a pharmacy's activity raise the kinds of 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 guidance states that FDA will consider enforcement action. In determining whether to initiate such an action, the guidance states that the Agency will consider whether the pharmacy engages in any of the following acts:

1. Compounding, except in very limited quantities, of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions.
2. Distributing inordinate amounts of compounded products out of State.
3. Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA sanctioned investigational new drug application (IND) that is in effect in accordance with section 505(1) of the Act and 21 CFR 312.
4. 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.
5. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendial (USP monograph) requirements.
6. Using commercial scale manufacturing or testing equipment for compounding drug products.
7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other State-licensed persons or commercial entities for resale.
8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. 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, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.

9. Failing to operate in conformance with applicable State law regulating the practice of pharmacy.

The above list of factors is not intended to be exhaustive, as other factors may be appropriate for consideration in a particular case.

Although the CPG was immediately effective when it was issued in May 2002, the Agency indicated it would be interested in receiving public comments on the guide. FDA received public comments and is in the process of revising the CPG in response to the comments. The Agency plans to publish a new draft of the CPG and will seek comments on it.

LIMITED FDA SURVEY OF COMPOUNDED DRUG PRODUCTS

Since 1990, FDA has become aware of more than 55 product quality problems associated with compounded products, many of which resulted in product recalls. In 2001, FDA's Division of Prescription Drug Compliance and Surveillance conducted a limited survey of drugs compounded by 12 compounding pharmacies that allowed compounded products to be ordered over the Internet. The goal of the survey was to gather information on the quality, purity, and potency of compounded drug products in the marketplace. The compounded products surveyed were selected from a cross-section of commonly compounded dosage forms based on FDA's assessment of the potential health risks resulting from improper compounding. FDA collected the samples via air mail order in the same manner a consumer would order the products over the Internet.

The 29 products sampled included hormonal products, antibiotics, steroids, anesthetics and drugs to treat glaucoma, asthma, iron deficiency anemia, and erectile dysfunction. Five different dosage forms (i.e., sterile injectables, ophthalmic products, pellet implants, inhalation products, and oral dosage forms) were sampled.

Ten (34 percent) of the 29 sampled products failed one or more standard quality tests performed. Nine with failing analytical results failed assay (potency) testing, with a range of 59 percent to 89 percent of expected potency.

Each year, FDA routinely samples drug products made by commercial manufacturers and analyzes these samples in FDA laboratories. More than 3,000 products from commercial manufacturers have been sampled and analyzed by FDA since fiscal year 1996. The analytical testing failure rate for commercially produced samples has been less than 2 percent for all tests, but for assay (potency) tests there were 4 failures out of 3,000. Compared to the 2 percent failure rate, the percentage of sampled compounded products failing analytical testing in our 2001 survey (34 percent) was higher than expected. Although the 2001 survey had several limitations including a small sample size, it provided valuable preliminary information on the quality of selected compounded drug products currently marketed. We believe that these laboratory results need to be interpreted cautiously and should not be generalized beyond the particular drugs and pharmacies involved. Further, we believe that the results call for additional study and consideration by FDA, the State regulatory authorities, professional organizations, and pharmacies.

OUTREACH ACTIVITIES

FDA has interacted on many occasions with stakeholders involved with pharmacy compounding. We have attended the annual meetings of the International Academy of Compounding Pharmacists participating on panels with representatives of the American Pharmacists Association (APhA), NABP, the USP, the National Association of Community Pharmacists, and others. In addition, we met separately with many of these stakeholders seeking to find common ground in how to approach the regulation of pharmacy compounding. We have participated in stakeholder meetings sponsored by the USP to address various initiatives including the accreditation of pharmacies that compound medications.

POSITIVE ACTIONS AND CHALLENGES

Some of the stakeholder groups with whom we have interacted are engaged in activities intended to provide greater confidence in the quality of compounded medications. For example, the NABP has a model code governing pharmacy compounding that substantially has been adopted by 10 States. The model code provides State Boards of Pharmacy with a framework for developing requirements for compounding pharmacies. The USP has developed a new chapter in the U.S. Pharmacopeia addressing sterile drug compounding practices. The chapter sets standards for the preparation of sterile compounded drugs. The American Society of Health-System Pharmacists also has such guidelines. The APhA, NABP, and USP have been discussing the possibility of developing an accreditation program that would set standards for and monitor compounding pharmacies. All of these activities are positive

steps in ensuring that pharmacy compounding is done with appropriate protections for patients, and we support them.

FDA recognizes that States have the direct ability to regulate pharmacy compounding and direct access to prescription records. However, limited State resources and varying standards and regulatory requirements are factors that affect the adequacy of State regulation. Pharmacy self-inspection is allowed in four States, which consists of pharmacist self-evaluation by questionnaire of the pharmacy's compliance with laws and regulations. In addition, there is variability in commitment to regulate pharmacy compounding among the States. Sometimes there is conflict between State Boards of Pharmacy and Health Departments based on disparate regulatory philosophies.

Clearly, when pharmacy compounding more closely approximates commercial manufacturing, FDA has an interest in regulating that practice as it does all other drug manufacturing. One difficult issue is where to draw that line. If the line is to be drawn based on volume, how much volume makes a compounder a manufacturer? There are many large compounding pharmacies, some of which are exclusively drug compounders. Similarly, there are many small drug manufacturers that snake drugs under approved new drug or abbreviated new drug applications. Through our review of these applications, we ensure that the drugs are safe and effective and that the processes by which the drugs are made produce consistently high quality products that maintain their safety and efficacy throughout their shelf life. This system of evidence-based medicine provides public health benefits to American consumers and health professionals because patients are able to rely with confidence on the medications they take and avoid ineffective therapies or those for which the risks do not exceed the benefits.

It is important to ensure that the production of drugs in pharmacy compounding does not undermine the incentives to develop and submit new drug applications to FDA with evidence of the safety and efficacy. At the same time, we recognize that pharmacy compounding is necessary where there is a medical need of a particular patient for a product that is not commercially available in an approved form. We must exercise our regulatory authority in such a way as to support pharmacy compounding that is necessary, while curbing abuses.

With this in mind, we can describe a few key areas where the Agency has taken action and where we believe a Federal role is appropriate:

• First, as a result of FDAMA, we developed a list of drugs that were inappropriate for compounding because they have been withdrawn from the market for safety reasons. In many cases, FDA reviewed the data concerning adverse events from our spontaneous reporting system and other databases and determined that the risks for these drugs exceeded the benefits for the uses to which they were approved. FDA has access to nationwide and global data concerning adverse events and we have the expertise to evaluate the risks of a therapy in relation to its benefits. Once FDA has determined that the risks of a therapy exceed its benefits to the extent that the drug should be removed from the market, it would be inappropriate to expose patients to the risks of the product by allowing compounding of that drug. FDA intends to continue to maintain this list and take action against pharmacies that compound unsafe products. Similarly, if FDA has specific information about significant potential risks associated with compounding a particular drug (e.g., one that was considered for but denied FDA approval), FDA may take action against such compounding, preferably in support of, or in conjunction with, the State authorities. Furthermore, FDA has continuing concerns about compounding, without an investigational new drug application in effect using ingredients that are "experimental" or not components of FDA approved drugs.

• Second, FDA believes it is in the best position to address the quality of bulk drug substances used in compounding. Many of these drugs are imported from abroad and individual States are unlikely to have the ability to conduct inspections of foreign producers and ensure the quality of these active ingredients in compounded products. As addressed in the CPG, drugs should not be compounded using active ingredients that were manufactured at facilities that are not even registered with FDA or that fail to meet accepted USP compendia) standards for quality.

• Third, FDA believes it is appropriate for the Agency to continue to investigate allegations of poor quality compounded drugs, in conjunction with the States, whenever possible. However, we also must act without States when State involvement is not forthcoming because of resource constraints or for other reasons. For example, an Internet or mail order pharmacy might be operating in a State with few resources for pharmacy inspections, but shipping poor quality compounded products nationwide. In such cases, FDA believes it plays an important role in addressing these dangerous practices. FDA believes that when issues regarding the quality of compounded drugs are significant enough to raise public health issues, FDA should

continue to play a role in working with the States to address these public health matters, and in the event that a State is unwilling or unable to join FDA, then the Agency in some cases must be allowed to unilaterally protect the public health from compounded drugs that pose unreasonable risks.

• Finally, the Agency should be able to determine when a pharmacy crosses the line between appropriate pharmacy compounding and manufacturing.

CONCLUSION

In summary, FDA welcomes this committee's interest in pharmacy compounding and would like to assure the committee that the Agency's efforts to address pharmacy compounding issues are designed to balance the need to allow legitimate forms of pharmacy compounding with the need for Federal oversight when pharmacy compounding threatens to compromise public health.

This concludes my testimony, Mr. Chairman. I will be glad to answer any questions you may have.

PREPARED STATEMENT OF STEVEN F. HOTZE, M.D.

Federal intervention into the practice of pharmacy, specifically compounding pharmacy, would prove detrimental to the health of Americans.

As a physician who has used compounded pharmacy medications for years, and who currently owns a compounding pharmacy, I have a unique perspective on the need to insure that compounded drugs are readily available to patients who need them. It is common for a doctor to determine that prescription drugs off the shelf are not adequate to meet the medical needs of an individual patient. This is where compounding pharmacy helps insure the individualized treatment that patients both need and demand. For this reason, I am somewhat concerned that this important sector of medical care is not better represented on the formal witness panels today to address more adequately the questions you may have.

The Food, Drug, and Cosmetic Act (FDCA) of 1938 established the authority of the Food and Drug Administration (FDA) over the pharmaceutical manufacturing of drugs. Pharmacies were specifically exempted from FDA regulation and their governance was relegated to the various State boards of pharmacy. At that time, all pharmacies practiced the compounding of medications. Pharmacies, including compounding pharmacies, should remain under the regulation of the States.

This hearing is the result of public outcry to the actions of a Kansas City pharmacist who violated State laws in reconstituting chemotherapeutic medications, a task which is not a compounding pharmacy procedure. His criminal actions were uncovered. He was stripped of his license and is currently serving time in prison. This isolated incidence had nothing to do with the practice of compounding pharmacy and does not provide a compelling argument for a Federal investigation, much less Federal intervention into the practice of pharmacy.

The issue is really philosophical. The FDA and its supporters believe that the Federal Government can ensure the public's health safety by acquiring jurisdictional authority over pharmacies, specifically compounding pharmacies. This flies in the face of the facts. According to an article published in the July 26, 2000 issue of the Journal of the American Medical Association, 106,000 individuals die each year in hospitals due to non-error, adverse effects of FDA approved, doctor prescribed medication. Fully 225,000 individuals die annually due to iatrogenic, treatment based, causes. This is the 3rd leading cause of death in America. Millions more suffer severe side effects from medical treatment. In these cases, the adage, that the "treatment is worse than the disease", rings true.

May I recommend that this Senate committee investigate the role of FDA approved drugs and iatrogenic causes leading to the deaths of 225,000 Americans annually.

There are others, who believe that most pharmacists, like others in business, realize that their self-interest is best served by operating their enterprises with the interests of their customers in mind. To do otherwise would result in a loss of business. State laws address the issue of fraudulent and dangerous business practices. State boards of pharmacy establish guidelines for safely conducting pharmacy practices and procedures. Ultimately, the pharmacist is responsible for his or her own behavior. Regulatory agencies cannot prevent an individual from committing a criminal act. However, regulatory agencies can, and often do, adversely affect the efficient, safe and productive practice of businesses.

Pharmacists who specialize in compounding prepare customized medications in accordance with a doctor's prescription in order to meet the need of an individual patient. These medications, which are not produced by pharmaceutical companies, are prepared using FDA approved bulk products and are provided to meet specific

patient requirements. Through clinical experience, a physician may decide to use alternative delivery systems for a specific medication, e.g., suppositories, creams, gels, liquids or capsules. Some compounded medications are not commercially available in the strength requested by the physician. In other cases, a patient may be allergic to the dyes, additives or excipients found in drugs produced by pharmaceutical manufacturers. In this case the solution would be the preparation of a compounded product without the allergy causing ingredients. Compounding pharmacy allows physicians and pharmacists to provide patients with alternative therapies otherwise not commercially available.

The recent results of the Women's Health Initiative study demonstrate the danger of drug company, FDA-approved, counterfeit hormones. Compounding pharmacies are able to offer physicians a natural, safe and effective treatment for women in midlife. That treatment is biologically identical hormone therapy that provides women with the same hormones that their bodies used to produce or currently produce in less than adequate amounts. With the baby boomer population aging, there are millions upon millions of women who would benefit from the replenishment of these hormones, enabling them to obtain and maintain health and wellness, naturally.

This is what concerns me about this hearing. The FDA has openly expressed its goal to regulate compounding pharmacies as manufacturers. At the June 2003 meeting of the International Academy of Compounding Pharmacists, two FDA regulators, Jane Axelrad and David Horowitz, clearly stated their intent to reclassify compounding pharmacies as manufacturers based upon the volume of prescriptions compounded. If this were to be implemented, then the FDA would require new drug applications (NDA) for compounded products in those pharmacies which exceeded their volume guidelines. To acquire an NDA costs hundreds of millions of dollars per product and the process takes 8–10 years. If the FDA were to be given regulatory power over compounding pharmacies, then they would end up classifying many large compounding pharmacies as manufacturers, thus driving them out of business. This would drastically limit the availability and affordability of compounded products to the public. More specifically, this would have a tragic effect on women in midlife who need biologically identical hormone therapy.

In the broad scheme of things, compounding pharmacies are part of the solution in providing needed care to millions of patients. While regulation at the State level can be improved, we need not to lose sight of the fact that over regulation of the compounding pharmacy profession could result in the denial of the very care and well being of our citizens of which this committee is vitally interested.

In summary, pharmacies, including compounding pharmacies, should continue to be regulated by their State boards of pharmacy.

Thank you for giving me the privilege of presenting my written testimony on behalf of compounding pharmacies.

PREPARED STATEMENT OF SARAH L. SELLERS, PHARMD MPH CANDIDATE, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

Mr. Chairman and Members of the Committee, thank you for the opportunity to speak with you today about the serious public health implications of pharmacy compounding—a topic which has been the focus of my professional practice and research for the past 8 years.

I am a licensed pharmacist with a specialization in sterile compounding. I have served as a member of the FDA's Advisory Committee on Pharmacy Compounding—a committee established to assist with the implementation of Federal pharmacy compounding regulations under the 1997 FDA Modernization Act. I am currently completing my Master of Public Health degree at Johns Hopkins Bloomberg School of Public Health, with a focus on pharmacoepidemiology and drug safety within the Department of Health Policy and Management.

More recently, I have established a small non-profit organization to study, analyze and communicate drug safety issues to concerned stakeholders.

I have survived two cancers and have lived with chronic rheumatic disease since my early childhood. I have come to rely on the exceptional quality of federally regulated pharmaceuticals from both a personal and professional perspective—the basic assurances to public health and safety provided by the Federal Food, Drug, and Cosmetic Act, that all citizens rely on, should not be undermined.

Over a decade ago, I began my career as a community pharmacist with a homecare pharmacy that provided injections to patients for administration in their homes. The pharmacy was making purportedly sterile injections from scratch using non-sterile ingredients. When I asked permission to order and substitute FDA-approved products because of safety concerns, I was cautioned that it would be less

profitable for the pharmacy. At that time, a sterile drug for continuous intraspinal infusion had an acquisition cost of approximately $400.00. However, using non-sterile, raw chemical ingredients the drug could be made for less than $10.00. Although Medicare reimbursed close to $1,000.00 for the drug at the time under Medicare Part B, profits could be maximized by making the drugs from scratch. The compounded dosage forms did not undergo a validated sterilization procedure, were not tested for potency or purity, and the risks of using such a product were not identified, analyzed or communicated to physicians or their patients. This emerging practice concerned me for both medical and ethical reasons—patients were unknowingly exposed to drugs that did not meet strict Federal standards for safety and efficacy, manufacturing or labeling to ensure safe use. I quickly learned that my experience was not unique—the practice was becoming "standard of care" in certain medical settings.

In 1998 I was appointed to the FDA's Advisory Committee on Pharmacy Compounding. During the implementation process, a group of compounding pharmacies challenged advertising restrictions in the new law, which led to a U.S. Supreme Court ruling that ultimately resulted in the nullification of *Section 503a of FDA Modernization Act* and the return of pre-FDAMA enforcement discretion on the part of the FDA. The absence of Federal compounding regulations has created vulnerabilities in our gold standard system for pharmaceutical regulation. Currently, compounding regulations are disparate and minimally enforced at the State level. Moreover, FDA simply does not have the information or resources to track down violative pharmacy compounding operations.

What is Traditional Pharmacy Compounding?

On a practical level, pharmacists are trained during their tenure in pharmacy school to convert tablets to liquids and to make topical formulations to meet exceptional medical needs that cannot be met with approved products. For instance, a 2-year-old transplant patient may require an anti-rejection medication that is only available in tablet form. In such a case, the tablet may be reformulated into an oral liquid for administration—such a medication would be considered life-sustaining and the expected benefits would likely outweigh risks associated with the use of an unlicensed product.

What is Contemporary Pharmacy Compounding?

Contemporary pharmacy compounding represents an emerging, substandard drug industry that exploits the traditional role of compounding by taking advantage of current loopholes in the law and resource constraints with regulators. The industry is supported and driven by profiteering distributors that supply chemicals (including active and inactive ingredients), equipment (including industrial size mixers, capsule and tablet machines), recipes, training and marketing tools for compounding pharmacists. This has resulted in the emergence and growth of a substandard industry of unregulated drug manufacturing, marketing, promotion and sales throughout the U.S. Recently, *Reuters Health* reported an estimate of 3,000–4,000 compounding pharmacies nationwide [2]—some of which dispense over 100 unregulated, compounded prescriptions per day. In some instances, compounding pharmacies have begun to attempt the tactics of mainstream drug manufacturers, and are seeking to employ sales representatives that would detail doctors about the availability and supposed benefits of their products.

What Are the Benefits and Risks of Contemporary Pharmacy Compounding?

The claimed benefits of contemporary compounding include creating patient specific and individualized dosage forms to meet any dosing requirement; providing varying strengths, sizes and shapes, dye-free, preservative free, and lactose free dosage forms; providing custom flavoring, and the provision of unavailable, unformulated and discontinued items; and providing increases in profitability for pharmacies and medical practices. Such benefits are broadly marketed through advertisements over the Internet, directly to physicians through professional detailing, and through the media. But such advertisements do not meet Federal requirements for presenting balanced information on risks. Pharmacists, through such advertisements, misuse the public trust in pharmacy and place patients and prescribers at a significant disadvantage for selecting safe and effective treatments. Physicians have come to expect products to be uniform in quality and may not appreciate the risks that are enhanced or created with compounded agents.[3]

The full range of risks associated with the use of compounded drugs have not been identified, analyzed or communicated to patients or prescribers. Section 502(n) of the FD&C Act requires that a manufacturer include a summary of risks in advertising—all materials and statements, including press materials, oral statements,

and sales materials for managed care organizations and hospitals must meet FDA requirements for truthfulness, fair balance and full disclosure.[6] Compounded drugs do not meet such requirements—promotional information for drugs made by pharmacists is devoid of risk information.

The true benefits of contemporary compounding may be financial. In a recent Medicare fraud case involving the mass manufacturing of adulterated and misbranded respiratory drugs an underlying reason for compounding was explained by a witness who said "*it is cheaper to make a compound solution and sell this medication than to buy an industrial product from an authorized supplier, it is much more expensive, so the profit you are going to obtain with a brand is much less than the one you are going to obtain with compounding. That is the reason for compounding, it is only profit*."[7] In an article examining the acquisition cost of respiratory drugs which appeared in the homecare trade journal *HME News*, a compounding supplier noted that "*providers, especially small ones, will risk compounding before losing that kind of money*" and further acknowledged that "*it's illegal, but profitability often overrules what's legal and illegal*."[8] The article further notes that compounding would be difficult to detect because of how Medicare is billed "*Hence, there's no way for the FDA to know whether a provider is using the premixed drug or compounding the two drugs themselves*." The financial incentives to compound drugs raise serious concerns regarding conflict of interest for compounding pharmacists who promote their use. If physician self-referral is constrained under the Stark laws, so too should compounding pharmacist self referral be penalized and restrained. In a debate appearing in the Journal of the American Academy of Child and Adolescent Psychiatry, physicians disputed the rationale for compounded hormone treatments for use in adolescent patients and questioned the proprietary interests of compounding pharmacists who promoted their use.[9] [10] [11]

What Are the Public Health Implications of Contemporary PharmacyCompounding?

In 1996, former FDA Commissioner David Kessler, MD warned that exempting pharmacy compounding from provisions of the Food, Drug, and Cosmetic Act would create a shadow industry of unapproved drug manufacturing thus undermining the FDA's authority to protect the public from ineffective or unsafe products.[12]

Compounded drugs are produced outside our Federal regulatory framework and carry risks of subpotency, superpotency and/or contamination. Complete and unbiased information on the size and scope of the industry has not been generated—we cannot estimate with accuracy the exposures of patients to unapproved, pharmacy made drugs and the associated effects on morbidity and mortality.

The ability of States to adequately protect the public from substandard drug exposure may be confounded by discrepant, over-lapping and in some cases non-existent State regulations, a lack of resources and lack of will. Professional standards for sterile compounding have not been consistently applied,[14] [15] and newly introduced, enforceable standards issued by the United States Pharmacopeia are optional for State boards to adopt and enforce.[15]

Pharmacists Are Drug Experts, Not Manufacturing Experts

A recent letter to the American Journal of Health System Pharmacists noted that pharmacy curricula do not give attention to sterile compounding procedures, and that this deficit is more pronounced in the U.S. than in Europe.[16] Pharmacists who compound drugs may not understand the complex system of drug regulations that provide public health protections. For instance, a pharmacist may not know that a raw bulk chemical that has been manufactured for use in an oral dosage form may not meet specifications for use by the intravenous or intraspinal route of administration. Pharmacists may generalize that a particular filter will sterilize any solution, independent of the properties of the solution or potential adulterants present. John Perrin Ph.D., professor emeritus from the University of Florida confirms that "*Technology has been downplayed in pharmacy schools for the last 25 years; we are not training pharmacists to make value judgments on what can and cannot be compounded and yet compounding is the fastest growing branch of the profession*."[17] Indeed, a compounding pharmacy advertises "*No longer are you limited to 'standard' medicine. Your choices now include new routes of administration, dosage strengths, pharmaceutical combinations and the ability to develop new, potentially helpful compounds. Medicine can be as large as your imagination*."[18] In other words, if a physician can imagine it, a compounding pharmacist can make it—without prior approval for safety or efficacy, without adherence to current Good Manufacturing Practices and without adhering to labeling, marketing or advertising requirements.

Analyses of Compounded Drugs

How well do pharmacists exact specific dosages? A recent study of prescription dispensing errors found that pharmacy compounding errors had significantly more serious outcomes and that children are "*particularly at risk because of the increased potential for error in the preparation and use of liquids*." [19] Such concerns have been heightened by a recent FDA survey of compounded drugs which found a 34 percent failure rate for drugs analyzed for potency and/or purity—of those drugs that failed potency tests, more than half contained less than 70 percent of their labeled content.[20] An analysis of a pharmacy-compounded remedy for treating ulcer disease concluded that the mixture was not stable and would undergo hydrolysis rendering it partially inactive immediately after mixing.[21] Other published reports and studies have found super and sub-potency, unacceptable levels of microbial contamination and the presence of impurities in pharmacy-compounded drug products.[22 23] Of great concern, as of today over a million doses of pharmacy-compounded drug products distributed throughout the U.S. have been recalled for bacterial or fungal contamination.[24 25] These risks of pathologic contamination are particularly disturbing when one considers that the compounding industry targets respiratory and parenteral routes of administration, and particularly to the home care market which largely serves a vulnerable and immunocompromised elderly population.

Quality of Chemicals Used in Compounding

The quality of raw bulk chemicals used in compounding is suspect. Pharmacists generally do not have the ability to test chemicals for identity, potency, purity and/or contamination. Because the *1987 Prescription Drug Marketing Act's Pedigree Requirements* have not been implemented, the ability to trace the raw chemicals used in compounding back to original manufacturers for information on quality, packaging, storage and shipment conditions is demonstrably difficult.

A 2000 hearing before the House E&C Committee chaired by the Honorable Fred Upton cited compounding pharmacies as a primary route of entry for counterfeit bulk drugs: "*Lured by high prices and potential profits in the U.S., counterfeit bulks can get into our prescription drugs in several ways: (1) as imported ingredients to U.S. manufacturers; (2) as imported ingredients to pharmaceutical compounders; and (3) as source ingredients for Internet pharmacies marketing to the U.S. The counterfeiters use sophisticated methods such as preparing false labeling, containers, seals and certificates of analysis, or using a manufacturing process that differs from the filed manufacturing process*." [26] This problem has also been recognized by authorities in Canada—a notice was recently sent to pharmacies alerting pharmacists that non-compliant, raw bulk chemicals were being offered for sale to pharmacies for compounding.[27] A letter from the Commerce Committee requesting information from former FDA Commissioner Jane Henney, MD which preceded the hearing, cautioned that counterfeit bulk drugs: "*pose a real or potential health hazard because their manufacturer is often unknown*" [28] and that the "*impurity profile is [also] unknown, and the age, the storage, the manufacturing environment, or the synthesis of the product cannot be determined*" [28] creating a situation where "*no amount of finished product testing can build quality into the product*."[28] In the U.S., although surveillance is limited, large quantities of chemicals for use in compounding have been recalled because bulk drug packages contained the wrong chemical ingredient, and for potential contamination or failed purity tests.[29]

Compounding pharmacists have also expressed concerns regarding the quality of bulk chemicals available for compounding. A Kansas City, Missouri compounding pharmacy's website notes that "*inexpensive chemicals that are past or near expiration, with no independent verification, are available, but unacceptable to O'Brien Pharmacy*."[30] The same pharmacy however, has marketed a narcotic morphine sulfate injection for intraspinal administration that exceeds the physical solubility for the chemical under normal storage conditions.[31]

At Risk Populations

Certain patient populations may be exposed to unapproved, compounded drugs more than others. Marketing and advertising for compounded drugs targets special populations including pediatric patients for which reflavoring is often suggested to make medicines more palatable, respiratory care patients who require treatments with nebulizers, elderly patients and hospice patients who may require alternate dosage forms, women to whom specialized hormone treatments are marketed, and men for sexual dysfunction treatments. Compounded drugs are also marketed directly to physicians' offices to improve profit margins for providing in-office injections.

Much attention has been focused on the long term safety of hormone replacement treatments—recent epidemiologic studies have found increased risks for certain can-

cers. This new risk information is now communicated to prescribers and patients for weighing therapeutic options and in order to manage risks. Compounding pharmacies are using this new information to promote alternative, unapproved hormone treatments—a compounding pharmacy claimed: "*Women are no longer willing to accept the risks associated with synthetic hormones, and are searching for safer alternatives. An estimated two million women are now benefiting from natural 'plant-derived bio-identical' estrogens and progesterone.*"[32] There is no scientific substantiation for such claims. In fact, the hormone treatments marketed by compounding pharmacies may share similar or even greater risks—women are unknowingly receiving unproven, experimental therapies that may harm them in the absence of informed consent.

Adverse Events

The use of unregulated, pharmacy-compounded dosage forms has been associated with morbidity and mortality throughout the nation:

- An outbreak of bacterial meningitis in California was associated with compounded spinal injections—three patients died and eight were hospitalized.
- CDC warned physicians and health systems to consider substandard, compounded drug exposures in cases of unexplained infections following intraspinal or intra-articular injections after an outbreak of fungal meningitis was associated with compounded drugs—CDC further cautioned that health systems may not be aware that they are purchasing compounded drugs, thus actually requiring vigilance to prevent compounded drugs from inadvertently entering supply chains.
- Compounded spinal injections were associated with neurologic complications including paralysis in an epidemiologic cohort study of patients who received unapproved, pharmacy-compounded continuous intrathecal infusions.[23]
- Three cases of poisonings in children have been associated with unapproved drugs compounded for Attention Deficit Hyperactivity Disorder.[35 36]
- A 5-year-old died as a direct result of receiving an unapproved compounded drug for bed-wetting.[37]
- Two patients developed septicemia and were hospitalized after receiving compounded vitamin injections contaminated with bacteria.[38]
- Three patients were hospitalized in critical condition after receiving compounded thyroid remedies.[39]
- A cancer patient died after receiving a compounded injection of herbal tea.[40]
- A patient became blind after using compounded eye-drops that were not sterile.[20]
- A study comparing a compounded prostaglandin dosage form with a licensed product found a higher incidence of cesarean delivery associated with the compounded drug.[41]
- An estimated 4,000 cancer patients received diluted, sub-therapeutic chemotherapeutic agents compounded in Missouri.[31]

The above mentioned cases are considered the "tip of the iceberg" by public health experts because pharmacists, unlike licensed manufacturers, are not required to detect or report problems associated with compounded drugs they make. These problems have come to the attention of the public only when the numbers of persons affected by a single incident or the severity of an incident have been significant enough to gain the attention of the media—not through surveillance and vigilance.

Surveillance

Compounded drugs are hard to trace making it difficult to measure or assess overall efficacy and safety. A 1998 report in *Drug Topics* examined 285 clonidine poisonings that were reported to the Kentucky Regional Poison Center during a 6-year period. Clonidine was primarily prescribed for ADHD with the largest demographic age group of 1–3 years (99 children).[42] Because a pediatric dosage form for clonidine did not exist, much of what was being administered was likely compounded. Of serious concern, pharmacy compounded, sustained-release clonidine dosage forms have been marketed to prescribers—a physician's practical guide states: "*it has been recommended to substitute the usual nighttime clonidine dosing with a pharmacy-compounded clonidine sustained release form, made by compounding clonidine with a hydroxyl-propylmethylcellulose extended-release polymer or with guanfacine*"[43] The erratic and unpredictable release from a pharmacy-compounded, purportedly sustained-release dosage form or from simple calculation errors may contribute to observed cases of clonidine toxicity—such dosage forms have not been tested to confirm extended-release and pharmacokinetic profiles. Three cases appearing in the medical literature have associated pharmacy-compounded clonidine preparations with clonidine poisonings in children,[35 36] but such associations are difficult to make without adequate surveillance.

Cost

Pharmacists make more money when they dispense unapproved, compounded formulations.[44] The average gross profit for a compounded prescription is estimated at $31.50 based on 1998 figures. According to Thomas Kaye RPh, MBA with Blue Cross Blue Shield of Oklahoma, the frequency of prescribing and reimbursement claims for compounded drugs has been increasing for many plans in recent years—he cautions that incidents associated with the use of such unapproved products "*add to overall patient cost, as well as morbidity and mortality*."[45]

State Oversight

State Boards of Pharmacy oversight of pharmacy compounding is discrepant and regulations are minimally enforced. While some States have adopted compounding rules that provide some public health protections, other States permit unrestricted distribution of compounded drugs that are not dispensed pursuant to an authorized, unsolicited prescription.

New Federal Regulations Are Necessary

It is ironic that so much concern is currently focused on the importation of drugs from other countries that may not match our gold standard system of regulation for pharmaceuticals, while we have within our own borders a flourishing, unregulated drug industry that manufactures, markets, and sells substandard products throughout the U.S.

If we do not act in the interest of public health and safety now, the history of substandard drug exposures and the related morbidity and mortality that led to the Kefauver-Harris Drug Amendments of 1962 will be relived through contemporary pharmacy compounding.

Recommendations To Protect the Public From the Hidden Risks of Unregulated, Pharmacy Compounded Drugs

1. Disclosure to prescribers and patients that compounded drugs are not FDA-approved and consumers should be advised of alternative FDA approved products.
2. Disclaimer on all compounded drug containers: THIS DRUG HAS NOT BEEN TESTED OR REVIEWED BY THE FOOD AND DRUG ADMINISTRATION (FDA) FOR SAFETY OR EFFECTIVENESS AND HAS NOT BEEN PRODUCED IN A FACILITY MEETING GOOD MANUFACTURING PRACTICES GUIDELINES.
3. Requirement that prescribers be notified before a compounded product is dispensed.
4. Prohibition against the compounding of drugs too difficult to compound for safety reasons.
5. Strict pedigree requirements for all chemicals used in compounding.

Summary of Testimony

1. Pharmacy-compounded drugs do not meet Federal requirements for establishing safety and efficacy (21 U.S.C. § 355), for manufacturing (21 U.S.C. § 351(a)(2)(b)) or labeling for safe use (21 U.S.C. § 352(0(1)).
2. Accurate, complete and unbiased information about the size and scope of the compounding industry in the U.S. is not available.
3. Federal compounding regulations (1997 FDA Modernization Act Section 503a) were nullified through a U.S. Supreme Court ruling in 2002. Current State compounding regulations are inadequate to protect public health and safety and to prevent individual patient exposures to unacceptable risks.
4. Lack of oversight of the compounding industry has created avenues to introduce commercial quantities of unapproved drugs into the market place through wholesale transactions.[1]
5. Morbidity and mortality associated with compounded drugs has been observed but because pharmacists are not required to detect or report problems associated with drugs they compound, the known cases of deaths, injuries, exposures and recalls of dangerous products are considered "tip of the iceberg" by public health officials.[20 23 31 33 34 35 36 37 38 39 40 41]
6. To address this issue, Senator's Bond and Roberts have offered an amendment to the Senate version of the Prescription Drug and Medicare Improvement bill (S. 1) to establish an advisory committee within the FDA to examine whether patients are receiving necessary, safe, and accurate dosages of compounded drugs. This is a critical first step in examining the public health risks associated with this newly emerging industry.
7. New Federal legislation for pharmacy compounding is necessary to protect patients and preserve the integrity of our Federal system of regulation for drug approval, manufacturing, and safety.

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PREPARED STATEMENT OF DANIEL A. HERBERT

Good morning. Thank you for the opportunity to appear before you today and present the views of the American Pharmacists Association. I am Dan Herbert, a pharmacist and the President-elect of APhA. I have been in practice for 37 years and currently own three community pharmacies in Richmond, Virginia. Founded in 1852 as the American Pharmaceutical Association, we are the largest national pharmacist organization in the United States, representing more than 53,000 practicing pharmacists, pharmaceutical scientists, student pharmacists and pharmacy technicians. APhA members practice in virtually every area of pharmacy practice, including independent and chain community pharmacy, hospital pharmacy, nuclear pharmacy, long term care pharmacy, home health care and hospice.

Let me first provide APhA's support of the Committee's goal that patients receive safe and effective medications. As pharmacists, we rely upon quality products as the first step in our work to help patients make the best use of their medications. When providing a quality product involves tailoring a medication for an individual patient, we use our scientific training and education to compound the medication.

Compounding medications is an important component of pharmacy practice-mine and that of my colleagues. While it is challenging to quantify the actual number of APhA's members who engage in drug compounding activities on a regular basis, virtually all practicing pharmacists will be involved with compounding activities at some point during their career-and most practitioners engage in some element of compounding in each week of practice. APhA has a compelling interest in helping pharmacists, in collaboration with practicing physicians, compound drug formulations to meet the needs of patients. Our compounding activities are a critical component of the American health care system, allowing physicians to prescribe medication therapy to best meet the needs of their patients.

My comments today will provide a brief history of pharmacist compounding, a description of the important role it plays in our health care system, the challenging task of distinguishing between compounding and manufacturing, and ways in which we can attempt to appropriately protect our patients by improving the quality of practice and identifying and stopping "bad actors".

COMPOUNDING: A TRADITIONAL COMPONENT OF PHARMACY PRACTICE

Compounding is a traditional component of pharmacy practice; only the drugs, dosage forms, and equipment or techniques have changed as pharmacy practice has advanced. As noted in the Chronicles of Pharmacy, "[p]harmacy, or the art of selecting, extracting, preparing and compounding medicines from vegetable, animal, and mineral substances, is an acquirement that must have been almost as ancient as man himself on earth." The early practice of pharmacy required the compounding of virtually all medications, because there were few, if any, commercially available products. The need for compounded products has diminished with the founding of pharmaceutical companies, although the need for this practice still exists today. Because the preparation of an extemporaneous pharmaceutical dosage form is not a trivial exercise, our position is that when an FDA-approved, commercially available product can meet a patient's needs, it should be employed as the preferred course of action. However, when a patient's particular situation obviates the use of commercial products, the knowledge and skills of a compounding pharmacist can be extremely valuable, even lifesaving.

It is a fundamental responsibility of the pharmacy profession to extemporaneously compound quality prescription products for patients who have unique medication needs. Through their education and licensure, pharmacists assume an ethical obligation to the public to maximize the intended benefits of drug therapy while minimizing the unintended side effects and adverse reactions. Some states require licensed pharmacies to offer compounding services [see 49 Pa. Code δ 27.18(p)(2) (2003);

W. Va. Code St. R. δ 15-1-19.4 (2003)]. Compounding enables pharmacists to use their knowledge and expertise of medication use to produce individualized medications that meet patient needs and improve health outcomes. Without compounding, pharmacists and physicians would be limited to a "one size fits all" strategy, which would have a direct, immediate, negative impact on the ability of health care providers to provide care to patients.

COMPOUNDING NECESSARY FOR MANY PATIENTS

As I stated earlier, it is challenging to quantify the actual number of pharmacists who engage in drug compounding activities on a regular basis, virtually all practicing pharmacists will be involved with compounding activities at some point. The unique knowledge and skill set of pharmacists enables them to extemporaneously compound medications to individualize patient care through the preparation of patient-specific products.

Compounding allows pharmacists and physicians to address the health care needs of patients who do not fall within the range of commercially available dosage strength and formulations. Patient needs vary from extremely small doses and specific combinations of drugs, to preservative-free products, to liquid dosage forms, to delivery systems that are not commercially available. In many situations, large-scale manufacturers are unable to tailor-make a medication in a cost effective manner. Without compounding, many patients would not have access to the correct combination of ingredients, the appropriate dose and dosage form, or the best delivery system.

In addition to unique patient needs, manufacturing and market limitations may require medications to be compounded. For example, some therapies, such as hyaluronidase injection (used as an adjunct to ophthalmologic surgery) must be compounded because the therapies generate insufficient revenue to pharmaceutical companies to justify large-scale manufacturing. Other medications, such as radioactive drugs used to diagnose or treat cancers or other diseases, must be compounded because they do not have sufficient "shelf life" to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. And finally, many manufactured "finished pharmaceutical" products are only "finished" in the sense of being ready to ship and then store in the pharmacy. These products must still be compounded, or in some cases merely reconstituted, by the pharmacist to provide a dosage form suitable for a patient's treatment.

Compounding involves different activities in different pharmacy practice settings. It may mean the preparation of oral liquids, topicals, or suppositories; the conversion of one dose or dosage form into another; the preparation of specific dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, or pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting. Examples of some of the most common compounded products include lotions, ointments, creams, gels, suppositories, intravenously administered fluids and medications, total parenteral nutrition products, and oral suspensions.

Although compounding may be required in any pharmacy practice setting and for any type of disease, there are concentrations of compounding practice. For example, due to the nature of the care they provide, hospital pharmacies have historically had a strong compounding component to their practice. And due to the nature of the disease and/or the patient size or age, compounding frequently occurs for patients with cancer, for pediatric care, and for hospice care.

Compounding in the hospital setting is a vital service that addresses the unique needs of patients requiring highly individualized medications. The primary compounding activity in hospitals is the preparation of intravenous admixtures ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens. Because daily intravenous therapy is provided through compounding of medications, nearly every person who has ever been admitted to a hospital -and those who will be admitted today and likely in the future- has received a compounded medication. In fact, the immediate availability of extemporaneous compounding by a pharmacist provides the hospital physician with literally any form or strength of medication needed for a patient's specific needs.

Cancer patients frequently benefit from compounding pharmacists' knowledge and skills. Almost all chemotherapy involves drugs and drug combinations that are compounded, or at least reconstituted, by pharmacists. It is imperative that a patient receive the correct drug dosage based upon the patient's body size, the type of cancer, the size and type of tumor, and the clinical condition of the patient including their kidney and liver function. This can often only be accomplished by using compounded, patient-specific medication preparations.

The compounding of pediatric dosage forms has also been an area of extensive activity, because many drugs used to treat children are only available in adult dosage forms. As the Committee is aware, finding the right drug, dose and dosage form to treat sick children is a complicated task. This Committee has made great strides in establishing incentives to improve the utility of manufactured products in treating children, but frequently, compounding is the only available avenue to achieve

the desired clinical outcomes. Commercially manufactured products for adult use must be modified and compounded for use in children. It has been estimated that more than 40% of doses given in pediatric hospitals require compounding to prepare a suitable dosage form. Indeed, utilization of compounded medications is essential for the provision of medical care to hospitalized children.

As the Committee is aware, hospice programs provide care for patients near the end of their lives who can no longer benefit from curative treatment and generally have a life expectancy of six (6) months or less. Patients suffering from incurable cancer have very special needs. Relief of pain near the end of life is an important element of maintaining the dignity and comfort of a dying patient and their loved ones. Hospice pharmacists often use compounded medications to alleviate pain and to control nausea and vomiting for patients in the hospice setting. A problem for many hospice patients is that pain medications are not manufactured in the required dosages. If commercial products that provide the precise dose(s) required are not available, the hospice pharmacist can often remedy the situation by extemporaneously preparing an individualized product. Additionally, some patients are not physically capable of swallowing the number of commercially manufactured tablets or capsules required or cannot take medications orally. A pharmacist can address these issues by either compounding a stronger product, by transforming tablets or capsules into a liquid, or by creating a preparation that can be applied topically or delivered rectally.

CONTINUOUS QUALITY IMPROVEMENT

Pharmacy compounding conforming to the highest possible professional standards is essential to optimal patient care. But maintaining quality and advancing practice requires the profession to be vigilant, and continually improve our professional standards and regulatory efforts. One question that continues to plague the profession and our regulators-the state boards of pharmacy-is how to distinguish between compounding and manufacturing; with one practice regulated by state boards of pharmacy and the other process, by the Food and Drug Administration.

Compounding has traditionally been characterized by the triad relationship of the physician, pharmacist and patient; working together to individualize care for maximum patient benefit. Pharmacy compounding is performed in response to a prescription from a licensed prescriber, or in preparation for a reasonably anticipated prescription, based upon prior experience and expected needs of individual patients.

APhA supports the National Association of Boards of Pharmacy's (NABP) definition of compounding, which states:

> Compounding—The preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice or (ii) for the purpose of, as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed patterns. [emphasis added] (Good Compounding Practices Applicable to State Licensed Pharmacies, Subpart A. Park Ridge, IL:NABP, 1993.)

The profession's definition of compounding does not encompass the preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues. Rather, the definition supports our assertion that the purpose of pharmacist compounding is to prepare an individualized drug treatment for a patient based on an order from a duly licensed prescriber.

Manufacturing, on the other hand, is defined by NABP as follows:

> Manufacturing—The production, preparation, propagation, conversion or processing of a Drug or Device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or Labeling or relabeling of its container, and the promotion and marketing of such Drugs or Devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compound for resale by pharmacies, Practitioners, or other Persons. (Id.)

As clear as this difference may seem to the profession of pharmacy, it has been a difficult distinction to implement because of the complexity and range of legitimate compounding activities. In public comments, even the Food and Drug Administration has suggested that the difference between compounding and manufacturing is better represented by the intersection of two jagged jigsaw puzzle pieces rather than a straight line.

The fundamental difference between compounding and manufacturing, and the key element in making any such distinction, is the existence of a pharmacist/prescriber/patient relationship. This triad should control the preparation of a drug product. Furthermore, compounded drugs are not for resale, but rather, are personal and responsive to a patient's immediate needs. Conversely, drug manufacturers produce batches consisting of millions of tablets or capsules at a time for resale, while utilizing many personnel and large scale manufacturing equipment, without knowledge of the specific patient who will ultimately consume them.

There are numerous factors to consider in distinguishing the FDA-regulated practice of manufacturing from the state-regulated practice of compounding. Such factors-though none is exclusive-include the volume of compounding by a particular pharmacist or pharmacy, the number of different products being compounded, the scope of the pharmacist's and pharmacy's practice, and of course, the presence of individual prescriptions for each compounded product.

ONGOING ACTIVITIES; OPPORTUNITIES FOR THE FUTURE

As professionals, pharmacists continually strive to provide the best patient care possible, including continuous review of practices and taking steps to improve medication use and advance patient care. While some may assert that little is being done to advance and improve pharmacist compounding, they are mistaken. APhA publishes resources for pharmacists to improve the practice, including The Art, Science and Technology of Pharmaceutical Compounding and Trissel's Stability of Compounded Formulations. And I am currently chairing an APhA committee setting strategic directions for the profession-including compounding. In our year of meetings, we have proposed some steps for advancing compounding practice as part of our commitment to providing safe and effective pharmaceutical care to the citizens of this country.

One aspect of our committee's work to date is the preliminary categorization of compounding to distinguish the types of compounding a pharmacist should be prepared to provide based on our pharmacy education and training, from the types of compounding that may require enhanced education or perhaps accreditation or certification processes. Because compounding encompasses a broad scope of activities-from the preparation of rather simple lotions for application to the skin to the preparation of radiopharmaceuticals for injection imaging, this categorization is important in focusing quality improvement efforts and resources. Our committee is also considering a proposal that pharmacists identify all compounded products for patients, so that patients understand that they will be using a non-commercially available product prepared specifically for their needs.

Other groups are pursuing efforts to improve pharmacy compounding practice as well. The United States Pharmaceopeia (USP), the official drug standard setting body for our country, has a long history of addressing pharmacy compounding, especially in the area of sterile preparations. Various state boards of pharmacy are exploring changes in statute and regulation to more clearly articulate the boundaries of practice for pharmacists in their jurisdiction. In my home state of Virginia, legislation passed in the 2003 session made changes to our compounding requirements. Specifically, the legislation clarified that compounded products be prepared and dispensed pursuant to a prescription and in the context of a bona fide practitioner-patient-pharmacist relationship; or in expectation of receiving a valid prescription based on observed prescribing patterns. All compounded products must be labeled and include a beyond-use date. In addition, a pharmacist is required to maintain and comply with a policy and procedure manual if their practice involves compounding products that are at high risk for contamination, radiopharmaceuticals, or dose-critical or specialized preparation dosages.

And APhA and other representatives of the profession of pharmacy are evaluating the issue and proposing solutions as well. In collaboration with the National Association of Boards of Pharmacy and the United States Pharmacopeia, our groups have recommended exploring the value of voluntary programs to improve compounding activity in certain categories. For example, should pharmacists engaged in compounding complex sterile products-such as those prepared from nonsterile bulk chemicals-have their pharmacy practice complete a site accreditation process to assess the policies and procedures employed? Should pharmacists engaged in other complex compounding activities complete specific training and education programs, or even an individual certification process to demonstrate their knowledge and skills? While this work is early in development, we are making progress and will continue our work to assure that patients get the compounded medications they need, at the level of quality they should expect.

Improving our efforts to provide quality compounded products will require collaborative efforts of consumers, the profession, state boards of pharmacy, and the FDA. Each stakeholder has an expertise that is essential in assuring the continued availability of this practice with the quality patients deserve. Consumers must play a role in all of our efforts, as we are pursuing this work for them. The profession must take the lead in guiding the regulatory agencies in how to draw the line between compounding and manufacturing, and in developing guidelines and voluntary accreditation or certification processes to demonstrate compliance with those guidelines. The state boards of pharmacy, responsible for regulating the profession, should maintain their primary regulatory role of pharmacy practice, including compounding, and will likely be tasked with new initiatives to enhance current regulatory efforts. The FDA has a role in regulating manufacturers, as well as defining some broad guidance, such as the identification of substances that should not be used in manufacturing or compounding because the substances have been withdrawn from the market for safety and efficacy concerns. All of these efforts require collaboration, coordination, and ongoing communication.

Through compounding, pharmacists fulfill a legitimate and essential need -providing patients with medications tailored to their needs. The professional education and training of pharmacists provides the unique knowledge and skills necessary to fulfill this health care need. The profession continues to research the most stable and appropriate mechanisms to produce compounded products, utilizing available and emerging technologies. By working together, prescribers and pharmacists help patients access otherwise unavailable therapies such as cream for breast cancer patients' radiation burns, or anticonvulsants in a suppository form when patients' veins are not accessible for injection. Without compounding, many physicians, pharmacists and patients would lose access to valuable treatments.

APhA supports the Committee's efforts to discuss this important issue. Pharmacist compounding improves patients' lives every day, but we must continually improve our practices to provide the best patient care. Pharmacists are ready to partner with stakeholders to develop effective strategies to improving the quality of compounding practices. APhA appreciates the opportunity to share the perspective of pharmacists on this issue.

PREPARED STATEMENT OF KEVIN KINKADE

Mr. Chairman, and Members of the Committee: I am pleased to be here today to be able to discuss with you the important issues surrounding the proper regulation of the role of pharmacists in the areas of compounding of pharmaceutical products. As I am sure all of you know, the art of compounding has been a traditional part of the practice of pharmacy for centuries. In fact, until after World War II when drug manufacturing became more prominent, compounding was one of the principal practices used to provide needed drugs to patients. While the need for compounding of products has changed since then, the importance of compounding certain products by prescription is still a very important and necessary part of the practice of pharmacy. Many physicians and patients across the United States depend on pharmacists to compound products that they need. This need may stem from different factors such as allergies to a commercial product, availability of the needed drug delivery system or the lack of the availability of the drug commercially. In any case, present day compounding has taken on a larger role through the use of new technologies and in some cases can be successful in meeting the special healthcare needs of patients.

What regulators must realize is that due to the increased practice by some pharmacies of compounding medicines and due to the complexity of some of these compounds, state law and resources can be challenged. State standards for compounding must be maintained as broad enough to encompass all areas of compounding that can occur yet also remain specific as to what requirements must be met in order to ensure safe and effective products are always provided to consumers.

MISSOURI BOARD OF PHARMACY

The board of pharmacy is comprised of seven members. Five members are full time practicing pharmacists from various practice settings within the state. One member, by law, must be a full time pharmacist employed in an institutional setting such as a hospital or long term care facility. One member is a consumer with no ties to the pharmaceutical industry. The board licenses and regulates pharmacists, pharmacies, drug distributors (wholesalers, manufacturers) and registers technicians. The field staff consists of seven inspectors who are all licensed pharmacists. The executive director, who is also a licensed pharmacist, is responsible for the operation of the board which includes the execution and management of all policy deci-

sions made by the board. The practice act for pharmacy in Missouri is Chapter 338 RSMo.

MISSOURI REGULATIONS GOVERNING COMPOUNDING

The Board of Pharmacy of the state of Missouri has regulated and enforced standards for the compounding of drugs through the promulgation of rules since their effective date of February of 1993 for sterile pharmaceuticals (4CSR 220-2.200) and April of 1996 for general compounding practices (4CSR 220-2.400). A need for such regulations was observed by the board due to 1) an increase in the number of pharmacies that were engaging in various forms of compounding which translated into an increase in the number of prescriptions being written and dispensed for such products and 2) the complexity of some of the compounded products and the concern for competent practices and standardization of formulas and procedures in pharmacies.

Several issues have warranted that the board review present standards again. The Robert Courtney case which was a criminal case of diluting compounded products for profit made headlines in Kansas City and all over the nation and had consumers, physicians and regulators wondering about the safety of the drug distribution system. While this case received tremendous publicity, it should not be considered the driving force that caused the board to change existing rules on compounding. Working on a major overhaul of the rules was already being considered. Proposals that had been either drafted or finalized by national organizations such as the United States Pharmacopoeia (Chapter 797) and the American Society of Health System Pharmacists were reviewed. Concerns over the competency of personnel preparing compounded products as well as adequate quality assurance measures within compounding practices was of chief concern. In addition, there was observed an increase in inter-state marketing and selling of compounded products by some pharmacies which seemed to border on manufacturing practices that would fall within the federal food, drug and cosmetic laws.

The standards for general compounding practices (4 CSR 220-400) were amended to include stricter definitions to better differentiate between the practice of compounding vs. manufacturing. Record requirements for compounded products were updated to include methods for compounding of the particular product and to track the source, lot number and the beyond use date of each drug product/ingredient used. A new section on the management of compounding was added that includes requirements for ensuring that products are pure and must be individually inspected before release to a patient. Pharmacies must also now have in place, a drug monitoring program that will evaluate compounding services through the monitoring of adverse reaction reports, infection rates, incidence of recalls and the tracking of complaints from prescribers and consumers. Recalls must be initiated when a product is deemed to be misbranded or adulterated. Prescribers of the product must be notified along with adequate information to take any corrective actions necessary. Patients must be notified when the recalled product could present a danger to patient health or safety. The board of pharmacy must be notified in the case of all recalls within three business days.

Standards for sterile product compounding were much more sweeping and required that the present rule be rescinded and a new, updated rule be promulgated in its place. Due to the complex and, in some cases, costly changes that the rule will require pharmacies to undergo, the effective date for compliance was selected as July 1st 2004. Strict definitions governing the equipment as well as the environment that such compounds are made in will require any pharmacy attempting to mix or create sterile compounds adhere to the highest standards of practice available in the present marketplace. The type of product produced as well as the storage time will govern the type of quality assurance procedures (process validation and testing of product) that must be included with every batch of product produced. Products that are compounded and considered to be of a low "risk" potential for adverse or untoward effects will require process validation. Those products considered to have a high risk potential in addition to process validation will need to be quarantined and tested by the pharmacy for sterility, pyrogenicity and potency. Examples of such products could include ophthalmic preparations and cardioplegic solutions. Depending on the expected shelf life of a product, pharmacies will have to arrange for an instrumental analysis of a product for a guarantee of potency.

MISSOURI TO BEGIN RANDOM TESTING OF COMPOUNDED PRODUCTS

Missouri has experienced several episodes of serious compounding misfortunes. As noted previously, the Robert Courtney case was of criminal conduct by one pharmacist to intentionally dilute compounded products that brought serious harm to

cancer patients. Such conduct was blatant and willful and is, as far as the profession of pharmacy is aware, the first case of its kind. Even so, state agencies responsible for the protection of consumers must be willing to consider changes in how standards are derived and enforced. In cases such as Courtney's, it is doubtful that any kind of state or federal inspection as we know today would uncover this type of criminal conduct. No amount of record reviews, inventory counts and reviews or equipment analysis would provide information that would lead to a discovery of this type of criminal conduct. Audits of drug inventories vs. usage have been suggested by some. However, the time and effort to audit the number of drugs in most pharmacies is simply not within the resources of any state or federal program.

This is where an idea for a system of randomized quality assurance can be of use. This past session of the Missouri legislature saw tight budgets and withholding of portions of agency appropriations in order to meet a constitutional requirement for a balanced budget. In this backdrop, the board was able to secure several areas of newly funded items, one of which, were funds for the testing of drug products that are compounded by state licensed pharmacies. Funding of approximately $159,000 was secured for this purpose. Such funds became available to the board on July 1st of this year.

Missouri law requires a bidding process to be completed in order to award an exclusive contract to a laboratory for the testing of compounds. Both sterile and nonsterile products will be tested for potency. Sterile products will also be tested for sterility and pyrogencicity.

While the amount of funds appropriated will not allow for consistent testing of the multitude of all compounded products provided to consumers, it will provide for randomized testing of products to 1) establish the level of competent practice patterns within a pharmacy or with a specific product class across a number of pharmacies and 2) in the remote chance that any pharmacist or pharmacy operation would contemplate a fraud on consumers, the randomization of the testing program would help dissuade such activities.

Funds from the appropriation will be used to pay a laboratory for testing of product samples and for reimbursing pharmacies for samples retrieved. Results of tests will be reviewed and, in most cases, shared with the pharmacy. When a test result is reported to be below existing standards for that product then a determination by the board will be made as to a course of action. This could include one or more of the following scenarios: 1) Retrieve more samples for further testing to see if multiple lots of the product are affected; 2) Should the result of a test reflect a potential harm if used by a consumer then explore what corrective actions to be executed on a voluntary basis by the pharmacy or by the board through discipline of the license or by restraining/injunctive court orders.

Over time, accumulated data could be analyzed to see if certain types of compounds do not meet the claims or benefits made for the products or that a specific pharmacy may not provide adequate services in order to competently compound a specific product or set of products.

The board does not believe that the system of testing described here will, by itself, guarantee that all products provided to consumers will be safe and effective. However, random testing and a thorough review of pharmacy compounding operations of pharmacies through adequate inspections will improve the chances that relevant standards for compounding of drugs are in place in those pharmacies that choose to provide such products. Anyone contemplating criminal fraud of consumers will have to consider these new policies and procedures as a real deterrent to offering or selling misbranded or adulterated products.

In summary, the board of pharmacy supports measures to secure additional resources to further voluntary compliance activity at the state level. Effective laws and sufficient appropriations need to be pursued in order to ensure adequate enforcement of state and federal drug laws. All fifty states maintain a board of pharmacy with the mandate of providing for the proper enforcement of laws in order to provide consumers with adequate minimum standards of practice. The profession of pharmacy should not be indicted for the outrageous and demoralizing acts of one individual. Criminal behavior must be dealt with separately from the enforcement of administrative laws over professional practice standards. While criminal acts within the profession are rare, they cannot be ignored. Measures that afford effective and random checks to licensees need to be the focus of boards of pharmacy who are in the best position to initiate and maintain adequate inspections of state licensed facilities. In addition, FDA should pursue by amendments to federal law or through the provision of an updated compliance guide, a strict definition of what is compounding vs. manufacturing and provide assistance in enforcement when violations of the act occur within interstate commerce.

In this regard, we would also urge the FDA to continue to work with the National Association of Boards of Pharmacy (NABP) in developing these definitions to maintain the appropriate balance of state and federal regulatory responsibilities and facilitate the implementation of the definitions across all states. Other components of state regulation of pharmacy compounding can be developed through NABP, working with the FDA, USP and other stakeholders. Incorporating these new definitions into NABP's Model State Pharmacy Act and Model Rules, which includes Good Compounding Practices Applicable to State Licensed Pharmacies, would also be encouraged as the Model Act has served as a useful guide to the states in the area of regulating compounding.

Thank you again for the opportunity to address this important issue today.

4 CSR 220-2.400 Compounding Standards of Practice

This rule defines compounding and establishes guidelines for the compounding of drugs.

(1) Compounding is defined as the preparation, incorporation, mixing and packaging or labeling of a drug or device as the result of a prescriber's prescription or prescription drug order based on the prescriber/patient/pharmacist relationship in the course of professional practice. Compounding may also be defined as the preparation, incorporation, mixing and packaging or labeling of a drug or device, for the purpose of, or as an incident to, research, teaching or chemical analysis and not for sale or dispensing purposes.

(2) Manufacturing is defined as the production, preparation, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or labeling or relabeling of its container, and the promotion and marketing of such drugs or devices.

(3) Batch compounded product is defined as a product compounded in advance of receipt of a prescription or a product compounded in a supply that will be used on more than one (1) dispensing to a patient or patients or any product compounded in excess of the filling of an individual prescription. A batch is a specific quantity of product compounded in a single, discrete process, by the same individuals, carried out during one (1) limited time period.

(4) Beyond-use date: A date after which a compounded preparation should not be used and is determined from the date the preparation is compounded. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates must be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

(5) Compounding Area and Equipment Requirements.

(A) The area(s) used for the compounding of drugs shall be maintained in a sanitary condition and shall be free of infestation by insects, rodents and other vermin. Trash shall be held and disposed of in a timely and sanitary manner.

(B) If drug products with special precautions for contamination, such as penicillin, are involved in a compounding operation, appropriate measures, including either the dedication of equipment for such operations or the meticulous cleaning of contaminated equipment prior to its return to inventory, must be utilized in order to prevent cross-contamination.

(C) Equipment used in the compounding of drug products shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. Equipment used in the compounding of drug products shall be of suitable composition so that surfaces that contact ingredients, in-process materials or drug products shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond that desired.

(6) Proper controls shall be maintained over drug products/ingredients, containers and container closures.

(A) Bulk drugs and other materials used in the compounding of drugs must be stored in adequately labeled containers in a clean, dry area or, if required, under proper refrigeration.

(B) Pharmacists shall only receive, store or use drug substances for compounding that have been made and/or distributed by Missouri licensed/registered drug distributors.

(C) Pharmacists shall only use nondrug substances for compounding that are free of any contaminants and which maintain full potency.

(D) Drug products/ingredients, containers and container closures used in the compounding of drugs shall be handled and stored in a manner to prevent contamination.

(E) Drug product/ingredient containers and container closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the compounded drug beyond the desired result. Container systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the compounded drug product.

(7) Appropriate quality control measures shall be maintained by the pharmacy and its staff over compounding methods.

(A) Such methods shall include the following and shall be followed in the execution of the drug compounding process. A separate log shall be maintained which includes:

1. Methods for the compounding of drug products to insure that the finished products have the identity, strength, quality and purity they purport or are represented to possess;
2. Date of compounding;
3. Identity of the compounding pharmacist;
4. A listing of the drug products/ingredients and their amounts by weight or volume;
5. Description of the compounding process and the order of drug product/ingredient addition, if necessary for proper compounding;

6. The identity of the source, lot number and the beyond-use date of each drug product/ingredient, as well as an in-house lot number and a beyond-use date for bulk compounded products; and

7. An identifying prescription number or a readily retrievable unique identifier for which the compound was dispensed.

(B) Information related to and the methods of compounding shall be available upon request.

(C) Pharmacists may compound drugs in limited quantities prior to receiving a valid prescription based on a history of receiving valid prescriptions that have been generated solely with an established pharmacist/ patient/prescriber relationship.

1. The compounding of drug products in anticipation of receiving prescriptions without an appropriate history of such prescriptions on file or a documented need, shall be considered manufacturing instead of compounding of the drug(s) involved. Limited quantities, for purposes of this rule, are further defined as an amount of batched product that represents a three (3)-month supply.

2. Creams, ointments, lotions, liniments or other compounded products intended for external use may be batched in the same manner as provided for in paragraph (5)(C)1. of this rule that represents a one (1)-year supply.

(D) Any excess compounded products shall be stored and accounted for under conditions dictated by its composition and stability characteristics to insure its strength, quality and purity. Excess product shall be labeled with the name of the drug(s), an in-house lot number and beyond-use date.

(E) Records as outlined in this rule shall be retained and made readily retrievable for inspection for two (2) years from the date of compounding.

(F) The actual name of each active or therapeutic ingredient contained in a compound shall be listed on the container of any product provided to a consumer.

(8) Management of Compounding.

(A) A pharmacist dispensing any compounded drug is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed and distributed properly. The pharmacist is responsible for ensuring that quality is built into the preparation of products, with key factors including at least the following general principles:

1. Personnel are capable and qualified to perform their assigned duties;

2. Ingredients used in compounding have their expected identity, quality and purity. Drug components must meet compendial standards or maintain a certificate of analysis on file when bulk drug substances are involved. Visual inspection of bulk drug substances must be performed;

3. Reasonable assurance that processes are always carried out as intended or specified;

4. Preparation conditions and procedures are adequate for preventing mix-ups or other errors; and

5. All finished products, as a condition of release, must be individually inspected for evidence of visible particulates or other foreign matter and for container-closure integrity and any other apparent visual defects.

(B) The pharmacy is responsible for developing a drug monitoring system for compounded products. The outcome monitoring system shall provide readily retrievable information suitable for the evaluation of the quality of pharmaceutical services. This shall include but not be limited to reported infection rates, incidence of adverse drug reactions, incidence of recalls and complaints from prescribers or clients.

(C) A recall must be initiated when a product is deemed to be misbranded or adulterated. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety.

1. In cases where the compounded product has the potential to harm the patient, the same recall notification, as provided for in this subsection, shall be provided to all patients that have received the recalled compounded product(s).

2. Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3) business days.

(9) Compounding of drug products that are commercially available in the marketplace or that are essentially copies of commercially available Federal Drug Administration (FDA) approved drug products is prohibited. There shall be sufficient documentation within the prescription record of the pharmacy of the specific medical need for a particular variation of a commercially available compound.

(10) Any alteration, change or modification to the contents of a commercially manufactured over-the-counter product shall require a prescription or prescription drug order from an authorized prescriber. The compounding of any drug product to be sold without a prescription is prohibited.

(11) Any person shown at any time, either by medical examination or pharmacist determination, to have an apparent illness or open lesion(s) that may adversely affect the safety

or quality of a drug product being compounded shall be excluded from direct contact with drug products/ingredients, drug product containers, container closures and in-process materials, until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of the products being compounded.

(12) Pharmacists shall not offer compounded drug products to other pharmacies, practitioners or commercial entities for subsequent resale or administration, except in the course of professional practice for a prescriber to administer to an individual patient by prescription. A pharmacist or pharmacy may advertise or otherwise provide information concerning the provision of compounding services; however, no pharmacist or pharmacy shall attempt to solicit business by making specific claims about compounded products.

(13) In addition to the requirements outlined in this rule, all standards and requirements as outlined in 4 CSR 220-2.200 Sterile Pharmaceuticals must be adhered to whenever compounding involves the need for aseptic procedures or requires the use of or results in an intended sterile pharmaceutical product.

AUTHORITY: sections 338.010, 338.140, 338.240 and 338.280, RSMo 2000. Original rule filed Aug. 25, 1995, effective April 30, 1996. Amended: Filed Dec. 3, 2002, effective July 30, 2003.*

**Original authority: 338.010, RSMo 1939, amended 1951, 1989 1990; 338.140, RSMo 1939, amended 1981, 1989, 1997; 338.240, RSMo 1951; and 338.280, RSMo 1951, amended 1971, 1981.*

4 CSR 220-2.200 Sterile Pharmaceuticals

PURPOSE: This rule establishes standards for the preparation, labeling and distribution of sterile pharmaceuticals by licensed pharmacies, pursuant to a physician's order or prescription.

(1) The provisions of sections (2)–(9) expire June 30, 2004.

(2) Definitions.

(A) Biological safety cabinet—containment unit suitable for the preparation of low to moderate risk agents where there is a need for protection of the product, personnel and environment, according to National Sanitation Foundation (NSF) Standard 49.

(B) Class 100 environment—an atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to Federal Standard 209B.

(C) Compounded sterile drug—a sterile drug dosage form that has been prepared by a pharmacist, to include a commercially prepared sterile drug dosage form which has been altered by a pharmacist.

(D) Cytotoxic Therapeutic Class—a pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the immune system and the alteration of the host's inflammatory response system.

(E) Parenteral—sterile preparation of drugs for injection through one (1) or more layers of skin.

(F) Sterile pharmaceutical—a dosage form free from living microorganisms (aseptic).

(3) Policy and Procedure Manual. A policy and procedure manual, as it relates to sterile products, shall be available for inspection at the pharmacy. The manual shall be reviewed and revised on an annual basis and shall include, but is not limited to, policies and procedures for any of the following services provided by the pharmacy:

(A) Clinical services;

(B) Cytotoxics handling, storage and disposal;

(C) Disposal of unused supplies and medications;

(D) Drug destruction and returns;

(E) Drug dispensing;

(F) Drug labeling/relabeling;

(G) Drug storage;

(H) Duties and qualifications for professional and nonprofessional staff;

(I) Equipment;

(J) Handling of infectious wastes;

(K) Infusion devices and drug delivery systems;

(L) Investigational drugs;

(M) Obtaining a protocol on investigational drugs from the principal investigator;

(N) Quality assurance procedures to include:

1. Recall procedures;

2. Storage and dating;

3. Educational procedures for professional staff, nonprofessional staff and patient;

4. Sterile procedures to include a log of the temperature of the refrigerator, routine maintenance and report of hood certification; and

5. Sterility testing;

(O) Record keeping;

(P) Reference material;

(Q) Sanitation;

(R) Security;

(S) Sterile product preparation procedures; and

(T) Transportation.

(4) Physical Requirements.

(A) Space. The licensed pharmacy shall have a designated area with entry restricted to designated personnel for preparing compounded, sterile products. This area shall be isolated from other areas and must be designed to avoid unnecessary traffic and airflow disturbances from activity within the controlled facility. It shall be used only for the preparation of sterile pharmaceutical products. It shall be of sufficient size to accommodate a laminar airflow hood and to provide for the proper storage of drugs and supplies under appropriate conditions of temperature, light, moisture, sanitation, ventilation and security.

(B) Equipment. The licensed pharmacy preparing sterile products shall have—

1. Appropriate environmental control devices capable of maintaining at least Class 100 conditions in the work area where critical objects are exposed and critical activities are performed; furthermore, the devices are capable of maintaining Class 100 conditions during normal activity. Examples of appropriate devices include laminar airflow hoods and zonal laminar flow systems of high efficiency particulate air filter (HEPA)-filtered air;

2. A sink with hot and cold running water and proper sewage disposal that is convenient to the compounding area for the purpose of hand scrubs prior to compounding;

3. Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious wastes from patients' homes;

4. When cytotoxic drug products are prepared, appropriate environmental control also includes appropriate biohazard cabinetry;

5. Refrigerator/freezer with a thermometer;

6. Temperature-controlled delivery container; and

7. Infusion devices, if appropriate.

(C) Supplies.

1. Disposable needles, syringes and other supplies needed for aseptic admixture;

2. Disinfectant cleaning solutions;

3. Hand washing agent with bactericidal action;

4. Disposable, lint free towels or wipes;

5. Appropriate filters and filtration equipment;

6. Oncology drug spill kit; and

7. Disposable masks, caps, gowns and sterile disposable gloves.

(D) Reference Library. The pharmacy shall have adequate current reference materials related to sterile products. Some suggested sources include: Handbook on Injectable Drugs, America Society for Hospital Pharmacists (ASHP); King's Guide to Parenteral Admixtures; United States Pharmacopeia (USP)/Negative Formulary (NF); American Hospital Formulary Service; Procedures for Handling Cytotoxic Drugs, American Society for Hospital Pharmacists (ASHP). In addition, the pharmacy shall maintain copies of current Occupational Safety and Health Administration (OSHA) requirements.

(5) Drug Distribution and Control.

(A) Medication Record System. A pharmacy generated medication record system must be separate from the prescription file. The patient medication record system shall be maintained under the control of the pharmacist-in-charge for a period of sixty (60) days after the last dispensing activity. The medication record system, at a minimum, shall contain:

1. Patient's full name;

2. Date of birth or age;

3. Weight;

4. Sex;

5. Sterile products dispensed;

6. Date dispensed;

7. Drug content and quantity;

8. Patient direction;

9. Identifying prescription number;

10. Identification of dispensing pharmacist;

11. Other drugs patient is receiving;

12. Known drug sensitivities and allergies to drugs and food; and

13. Primary diagnosis.

(B) Labeling (supplemental). Each sterile pharmaceutical dispensed to patients shall be labeled in accordance with section 338.059, RSMo and with the following supplemental information affixed to a permanent label:

1. Directions for administration including infusion rate, where applicable;

2. Date of compounding;

3. Expiration date and time;

4. Identity of pharmacist compounding and dispensing;

5. Storage requirements;

6. Auxiliary labels, where applicable; and

7. Cytotoxic drug auxiliary labels, where applicable.

(C) Records and Reports. The pharmacist-in-charge shall maintain, access to, and submit as appropriate, records and reports required to insure the patient's health, safety and welfare. These reports shall be maintained for two (2) years and shall be readily retrievable, subject to inspections by the State Board of Pharmacy or its agents. Such shall include, at a minimum, the following:

1. Purchase records;

2. Policy and procedure manual;

3. Training manuals, where applicable;

4. Policies and procedures for cytotoxic waste, where applicable;

5. Other records and reports as may be required by law and the rules of the State Board of Pharmacy; and

6. Information regarding individual patients shall be maintained in a manner to assure confidentiality of the patient's record. Release of this information shall be in accordance with federal or state laws, or both.

(D) Delivery Service. The pharmacist-in-charge shall assure the environmental control of all products shipped. A sterile pharmaceutical product must be shipped or delivered to a patient in appropriate temperature controlled delivery containers (as defined by USP standards) and assurances must be made that appropriate storage facilities are available. Chain of possession for the delivery of Schedule II controlled substances via couriers must be documented and a receipt required.

(6) Cytotoxic Drugs. The following additional requirements are necessary for those licensed pharmacies that prepare cytotoxic drugs to insure the protection of the personnel involved:

(A) All cytotoxic drugs should be compounded in a vertical flow, Class II biological safety cabinet. If used for other products, the cabinet must be thoroughly cleaned;

(B) Protective apparel shall be worn by personnel compounding cytotoxic drugs which shall include disposable masks, gloves and gowns with tight cuffs;

(C) Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile products;

(D) Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;

(E) Written procedures for handling both major and minor spills of cytotoxic agents must be developed and must be included in the policy and procedure manual; and

(F) Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(7) Quality Assurance.

(A) There shall be a documented, ongoing quality assurance control program that monitors personnel performance, equipment and facilities. Appropriate samples of finished products shall be examined to assure that the pharmacy is capable of consistently preparing sterile products meeting specifications. These examinations shall include: visual inspection under a direct light source in the preparation of products in order to determine the presence of inappropriate particulate matter or signs of deterioration; policies and procedures for monitoring of sterile products whereby any untoward effects exhibited by a patient that may be due to the product, are reported to the pharmacy; and appropriate samples are collected and microbial tests are completed to ascertain the presence of microbial contamination of suspect products. Quality assurance procedures shall include:

1. Recall procedures;

2. Storage and dating; and

3. Environmental procedures which include a log of the temperature of the refrigerator, routine maintenance and report of any hood certification.

(B) Clean Room and Hood Certification. All clean rooms and laminar flow hoods shall be certified by an independent contractor according to Federal Standard 209B or National Sanitation Foundation Standard 49 for operational efficiency at a minimum of every twelve (12) months. Certification records shall be maintained as a part of the pharmacy record.

(C) Prefilters. Prefilters for the clean air source shall be replaced on a regular basis and the replacement date documented.

(D) Nonsterile Compounding. If bulk compounding is performed utilizing nonsterile chemicals, extensive end-product testing, as referenced in the Remington Reference Manual, must be documented prior to the release of the product from quarantine. This process must include appropriate tests for particulate matter and testing for pyrogens.

(E) Expiration Dates. There shall be written justification of the chosen expiration date for compounded products. If a written standard is not available, a maximum of twenty-four (24) hours expiration date shall be used.

(F) Quality Assurance Audits. There shall be documentation of quality assurance audits at regular, planned intervals and should include infection control and sterile technique audits.

(8) Pharmacists and pharmacies where sterile compounding is provided may be exempt from this rule when that compounding is restricted to the following:

(A) The method of compounding utilizes compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product; or

(B) The amount of compounding provided by the pharmacy is for emergency situations. An emergency is defined as—

1. Situations where the sterile compound is needed and is unavailable from or inconvenient to obtain from other sources;

2. Compounding will be provided to the patient immediately and used within a twenty-four (24)-hour period; and

3. Products are provided to the patient as a single dosage unit and the drug is not intended to be provided beyond an immediate emergency period.

(9) This rule is not intended to include any pharmacy that provides sterile pharmaceuticals on a prescription order that has not been compounded by the pharmacy or had the packaging or labeling of the product altered by the pharmacy.

(10) The provisions of sections (11)–(26) become effective July 1, 2004.

(11) Definitions.

(A) Aseptic processing: The technique involving procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during processing.

(B) Batch: Compounding of multiple sterile product units in a single discrete process, by the same individuals, carried out during one (1) limited time period.

(C) Beyond-Use date: A date after which a compounded preparation should not be used and is determined from the date the preparation is compounded. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates must be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

(D) Biological safety cabinet: Containment unit suitable for the preparation of low to moderate risk agents where there is a need for protection of the product, personnel and environment, according to NSF International standards.

(E) Class 100 environment: an atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(F) Class 10,000 environment: An atmospheric environment which contains less than ten thousand (10,000) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(G) Clean room: A room—

1. In which the concentration of airborne particles is controlled;

2. That is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room; and

3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

(H) Clean zone: Dedicated space—

1. In which the concentration of airborne particles is controlled;

2. That is constructed and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone; and

3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

This zone may be open or enclosed and may or may not be located within a clean room.

(I) Compounding: For the purposes of this regulation, compounding is defined as in 4 CSR 220-2.400(1). Compounded sterile medications may include, but are not limited to, injectables, parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and ophthalmic preparations.

(J) Controlled area: For purposes of these regulations, a controlled area is the area designated for preparing sterile products. This is referred to as the buffer zone (i.e., the clean room in which the laminar airflow workbench is located) by the *United States Pharmacopoeia* (USP).

(K) Critical area: Any area in the controlled area where products or containers are exposed to the environment.

(L) Critical site: An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment.

(M) Critical surface: Any surface that comes into contact with previously sterilized products or containers.

(N) Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the immune system and the alteration of a host's inflammatory response system.

(O) Emergency dispensing: Is a situation where a Risk Level 3 product is necessary for immediate administration of the product and no alternative product is available and the prescriber is informed that the product is being dispensed prior to appropriate testing. Documentation of the dispensing of the product, the prescriber's approval for dispensing prior to the receipt of test results and the need for the emergency must appear within the prescription record. A separate authorization from the prescriber is required for each emergency dispensing.

(P) High-Efficiency Particulate Air (HEPA) filter: A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove ninety-nine point ninety-seven percent (99.97%) of all particles three-tenths (0.3) microns or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a Class 100 clean room.

(Q) Isolator (or barrier isolator): A closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits.

(R) Parenteral: A sterile preparation of drugs for injection through one (1) or more layers of skin.

(S) Process validation or simulation: Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product and with the same container or closure system.

(T) Quality assurance: For purposes of these regulations, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug products lead to products that meet predetermined standards of quality.

(U) Quality control: For the purposes of these regulations, quality control is the set of testing activities used to determine that the ingredients, components and final sterile products prepared meet predetermined requirements with respect to identity, purity, nonpyrogenicity and sterility.

(V) Repackaging: The subdivision or transfer of a compounded product from one container or device to a different container or device.

(W) Sterile pharmaceutical: A dosage form free from living microorganisms.

(X) Sterilization: A validated process used to render a product free of viable organisms.

(Y) Temperatures:

1. Frozen means temperatures between twenty below zero and ten degrees Celsius (−20 and 10°C) (four below zero and fourteen degrees Fahrenheit (−4 and 14°F)).

2. Refrigerated means temperatures between two and eight degrees Celsius (2 and 8°C) (thirty-six and forty-six degrees Fahrenheit (36 and 46°F)).

3. Room temperatures means room temperatures between fifteen and thirty degrees Celsius (15 and 30°C) (fifty-nine and eighty-six degrees Fahrenheit (59 and 86°F)).

(Z) Validation: Documented evidence providing a high degree of assurance that specific processes will consistently produce a product meeting predetermined specifications and quality attributes.

(AA) Definitions of sterile compounded products by risk level:

1. Risk Level 1: Applies to compounded sterile products that exhibit characteristics A., B., and C., stated below. All Risk Level 1 products shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product. Risk Level 1 includes the following:

A. Products:

(I) Stored at room temperature and completely administered within forty-eight (48) hours after preparation; or

(II) Stored under refrigeration for seven (7) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours; or

(III) Frozen for thirty (30) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours.

B. Unpreserved sterile products prepared for administration to one (1) patient or batch-prepared products containing suitable preservatives prepared for administration to more than one (1) patient.

C. Products prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals (e.g., from vials or ampules) obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers.

2. Risk Level 2: Sterile products exhibit characteristic A., B., or C., stated below. All Risk Level 2 products shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product and with closed-system transfer methods. Risk Level 2 includes the following:

A. Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30) days frozen or administered beyond forty-eight (48) hours after preparation and storage at room temperature.

B. Batch-prepared products without preservatives that are intended for use by more than one (1) patient.

C. Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer (e.g., automated compounder).

3. Risk Level 3: Sterile products exhibit either characteristic A. or B.:

A. Products compounded from nonsterile ingredients or compounded with nonsterile components, containers or equipment before terminal sterilization.

B. Products prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.

(12) Policy and Procedure Manual.

(A) A manual, outlining policies and procedures encompassing all aspects of Risk Level 1, 2 and 3 products, shall be available for inspection at the pharmacy. The manual shall be reviewed on an annual basis.

(13) Personnel Education, Training and Evaluation.

(A) Risk Level 1: All pharmacy personnel preparing sterile products must receive suitable didactic and experiential training.

(B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training includes assessment of competency in all Risk Level 2 procedures via process simulation.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, operators have specific education, training and experience to prepare Risk Level 3 products. The pharmacist knows principles of good compounding practice for risk level products, including—

1. Aseptic processing;

2. Quality assurance of environmental, component, and end-product testing;

3. Sterilization; and

4. Selection and use of containers, equipment, and closures.

(14) Storage and Handling in the Pharmacy.

(A) Risk Level 1 and 2: Solutions, drugs, supplies and equipment must be stored according to manufacturer or USP requirements. Refrigeration and freezer temperatures shall be documented daily. Other storage areas shall be inspected regularly to ensure that temperature and lighting meet requirements. Drugs and supplies shall be shelved above the floor. Removal of products from boxes shall be done outside controlled areas. Removal of used supplies from the controlled area shall be done at least daily. Product recall procedures must permit retrieving affected products from specific involved patients.

(B) Risk Level 3: In addition to Risk Level 1 and 2 requirements, procedures include procurement, identification, storage, handling, testing, and recall of components and finished products. Finished but untested Risk Level 3 products must be quarantined under minimal risk for contamination.

(15) Facilities and Equipment.

(A) Risk Level 1: The controlled area shall be separated from other operations. The controlled area must be clean and well lit. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected regularly. Sterile products must be prepared in at least a Class 100 environment (the critical area). Computer entry, order processing, label generation, and record keeping shall be performed outside the critical area. The critical area must be disinfected prior to use. A workbench shall be recertified every six (6) months and when it is moved; prefilters must be visually inspected on a regularly scheduled basis and replaced according to manufacturer's specifications. Pumps utilized in the compounding process shall be recalibrated and documented according to manufacturer procedures.

(B) Risk Level 2: In addition to all Risk Level 1 requirements, the controlled area must meet Class 10,000 clean room standards; cleaning supplies should be selected to meet clean room standards; critical area work surface must be cleaned between batches; floors should be disinfected daily; equipment surfaces weekly; and walls monthly; with applicable environmental monitoring of air and surfaces. Automated compounding devices must be calibrated and verified as to accuracy, according to manufacturer procedures. Clean rooms not utilized on a daily basis must be cleaned prior to use as stated above.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, products must be prepared in a Class 100 workbench in a Class 10,000 clean room, in a Class 100 clean room or within a positive pressure barrier isolator. Access to the clean room must be limited to those preparing the products and who are in appropriate garb. Equipment must be cleaned, prepared, sterilized, calibrated, and documented according to manufacturer's standards. Walls and ceilings must be disinfected weekly. All non-sterile equipment that is to come in contact with the sterilized final product must be sterilized before introduction in the clean room. Appropriate cleaning and disinfection of the environment and equipment are required.

(16) Apparel.

(A) Risk Level 2: In the controlled area, personnel wear low particulate, clean clothing covers. Head and facial hair is covered. Gloves, gowns, and masks are required. During sterile preparation gloves shall be rinsed frequently with a suitable agent and changed when integrity is compromised.

(B) Risk Level 3: In addition to Risk Level 2 requirements, clean room apparel must be worn inside the controlled area at all times during the preparation of Risk Level 3 sterile products except when positive pressure barrier isolation is utilized. Attire shall consist of a low-shedding coverall, head cover, face mask, and shoe covers.

(17) Aseptic Technique and Product Preparation.

(A) Risk Level 1: Sterile products must be prepared in a Class 100 environment. Personnel shall scrub their hands and forearms for an appropriate period at the beginning of each aseptic compounding process. Eating, drinking and smoking are prohibited in the controlled area. Talking shall be minimized to reduce airborne particles. Ingredients shall be determined to be stable, compatible, and appropriate for the product to be prepared, according to manufacturer, USP, or scientific references. Ingredients and containers shall be inspected for defects, expiration and integrity before use. Only materials essential for aseptic compounding shall be placed in the workbench. Surfaces of ampules and vials shall be disinfected before placement in the workbench. Sterile components shall be arranged in the workbench to allow uninterrupted laminar airflow over critical surfaces of needles, vials, ampules, etc. Automated devices and equipment shall be cleaned, disinfected and placed in the workbench to enable laminar airflow. Aseptic technique shall be used to avoid touch contamination of critical sites of containers and ingredients. Particles shall be filtered from solutions. Needle cores shall be avoided. The pharmacist shall check before, during, and after preparation to verify the identity and amount of ingredients before release.

(B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing formula, components, procedures, sample label, and final evaluation shall be made for each product batch. A separate work sheet and lot number for each batch shall be completed. When combining multiple sterile products, a second verification of calculations shall take place. The pharmacist shall verify data entered into any automatic compounder before processing and check the end product for accuracy.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, nonsterile components must meet standards if available, as verified by a pharmacist and a certificate of analysis. Batch preparation files shall also include comparisons of actual with anticipated yields, sterilization methods, and quarantine specifications. Presterilized containers shall be used when feasible. Final containers must be sterile and capable of maintaining product integrity throughout the shelf life. Sterilization methods must be based on properties of the product.

(18) Process Validation.

(A) Risk Level 1: All pharmacy personnel who prepare sterile products shall pass a process validation of aseptic technique before compounding sterile products. Pharmacy personnel competency must be reevaluated by process validation at least annually, whenever the quality assurance program yields an unacceptable result, or whenever unacceptable techniques are observed. If microbial growth is detected, the entire sterile process must be evaluated, corrective action taken, and the process simulation test performed again.

(B) Risk Level 2: In addition to Risk Level 1 requirements, process simulation procedures shall cover all types of manipulations, products and batch sizes.

(C) Risk Level 3: In addition to all Risk Level 1 and 2 requirements, written policies shall be maintained to validate all processes, procedures, components, equipment and techniques.

(19) Record Keeping.

(A) Risk Level 1: The following must be documented:

1. Training and competency evaluation of pharmacy personnel involved in sterile product preparation;
2. Refrigerator and freezer temperature logs;
3. Certification of workbenches;
4. Copies of any manufacturer standards that are relied upon to maintain compliance with this rule; and
5. Other facility quality control logs as appropriate including all maintenance, cleaning, and calibration records.

(B) Risk Level 2: In addition to Risk Level 1 requirements, records of any end-product testing and batch preparation records must be maintained.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, record requirements for Risk Level 3 products must include:

1. Preparation work sheet;
2. Sterilization records;
3. Quarantine records, if applicable;
4. End-product evaluation and testing records as required in section (22); and
5. Ingredient validation records as required in section (22).

(D) All records and reports shall be maintained for two (2) years and shall be readily retrievable, subject to inspections by the board of pharmacy or its agents.

(20) Labeling.

(A) Risk Level 1: Sterile products dispensed to patients shall be labeled in accordance with section 338.059, RSMo and with the following supplemental information affixed to a permanent label:

1. Beyond-use date;
2. Storage requirements;
3. Any device specific instructions; and
4. Auxiliary labels, when applicable.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.

(21) Beyond-Use Dating.

(A) Risk Level 1: All sterile products must bear a beyond-use date. Beyond-use dates are assigned based on current drug stability information and sterility considerations.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method for establishing all expiration dates, including laboratory testing of product stability, pyrogenicity, particulate contamination and potency. Expiration dating not specifically referenced in the product's approved labeling or not established by product specific instrumental analysis, shall be limited to thirty (30) days. Beyond-use dating not specifically referenced in the products approved labeling or not established by product specific instrumental analysis shall be limited to thirty (30) days. There must be a reliable method for establishing all beyond-use dating. Products maintaining beyond-use dating of greater than thirty (30) days shall have lab testing of product stability and potency.

(22) End-Product Evaluation.

(A) Risk Level 1: The final product must be inspected for container leaks, integrity, solution cloudiness or phase separation, particulates in solution, appropriate solution color, and solution volume. The pharmacist must verify that the product was compounded accurately as to the ingredients, quantities, containers, and reservoirs. Background light or

other means for the visual inspection of products for any particulate and/or foreign matter must be used as part of the inspection process.

(B) Risk Level 2: All Risk Level 1 requirements must be met.

(C) Risk Level 3: In addition to all Risk Level 1 requirements, the process validation procedure shall be supplemented with a program of end-product sterility testing according to a formal sampling plan. Samples shall be statistically valid to ensure that batches are sterile. A method for recalling batch products shall be established if end-product testing results are unacceptable. All sterile products must be tested for sterility. All parenteral sterile products must also be tested for pyrogenicity. Sterile products compounded from nonsterile components must be quarantined pending results of end-product testing.

1. Sterility testing: Sampling for the sterility test shall occur promptly upon the completion of preparation. The sterility test, including the sampling scheme, shall be conducted according to one (1) of the USP methods.

2. Pyrogen/Endotoxin testing: Each sterile parenteral product prepared from non-sterile drug components shall be tested for pyrogen or endotoxin according to recommended USP methods.

3. Potency: The pharmacy shall have a procedure for a pre-release check of the potency of the active ingredients in the compounded sterile product prepared from non-sterile bulk active ingredients. The procedure shall include at least the following verifications by a pharmacist:

A. The lot of the active ingredients used for compounding have the necessary labeling, potency, purity, certificate of analysis and other relevant qualities;

B. All weighings, volumetric measurements, and additions of ingredients were carried out properly;

C. The compounding or control records include documentation that the fill volumes of all units available for release were checked and were correct; and

D. The final potency is confirmed by instrumental analysis for sterile products that have been assigned a beyond-use date of more than thirty (30) days.

(D) Emergency Dispensing of a Risk Level 3 Sterile Product: When a compounded Risk Level 3 product must be released prior to the completion of testing, the sterile product may be dispensed pending test results.

(23) Handling Sterile Products Outside the Pharmacy.

(A) Risk Level 1: The pharmacist-in-charge shall assure the environmental control of all sterile compounded products shipped. Sterile products shall be transported so as to be protected from excesses of temperatures and light within appropriate packaging or delivery containers that maintain necessary storage conditions to preserve the quality and integrity of sterile products. The pharmacy shall follow written procedures that specify packing techniques, configuration, and materials for groups of products with common storage characteristics and for specific products where unique storage conditions are required to retain adequate stability and product quality.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.

(24) Cytotoxic Drugs.

(A) The following additional requirements are necessary for those licensed pharmacies that prepare cytotoxic drugs to insure the protection of the personnel involved:

1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet or an isolator. If used for other products, the cabinet must be thoroughly cleaned;

2. Protective apparel shall be worn by personnel compounding cytotoxic drugs which shall include disposable masks, gloves and gowns with tight cuffs;

3. Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile products;

4. Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious waste from patients' homes. Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;

5. Written procedures for handling major and minor spills and generated waste of cytotoxic agents must be developed and must be included in the policy and procedure manual;

6. Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(25) Exemption: Pharmacists and pharmacies where sterile compounding is provided may be exempt from this rule when compounding is restricted to utilizing compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product.

(26) In addition to the requirements outlined in this rule, all standards and requirements as outlined in 4 CSR 220-2.400 must be maintained.

AUTHORITY: sections 338.010, 338.140, 338.240 and 338.280, RSMo 2000. Original rule filed May 4, 1992, effective Feb. 26, 1993. Amended: Filed Oct. 28, 1994, effective May 28, 1995. Rescinded and readopted: Filed Dec. 3, 2002, effective July 30, 2003.*

**Original authority: 338.010, RSMo 1939, amended 1951, 1989, 1990; 338.140, RSMo 1939, amended 1981, 1989, 1997; 338.240, RSMo 1951; and 338.280, RSMo 1951, amended 1971, 1981.*

PREPARED STATEMENT OF WILLIAM P. KENNEDY, OWNER, NEPHRON PHARMACEUTICALS CORPORATION FDA-APPROVED MANUFACTURING FACILITY/ORLANDO

Mr. Chairman and Members of the Committee, thank you sincerely for your efforts to shed public light on the phenomenon in the country today of pharmacies boldly compounding massive quantities of prescription drugs. I believe that I am uniquely qualified to speak to you on this topic. I am both a licensed pharmacist who was involved in large scale compounding and I am now the owner of an FDA-approved manufacturing facility in Orlando, Florida. I know this issue inside out. The American public is at risk and you are to be commended for your interest in and pursuit of non-FDA compliant compounding.

In 1966 I graduated from the University of South Carolina's College of Pharmacy and became a registered pharmacist in that State. A year later, I moved to Florida and began to pursue my career in pharmacy in earnest.

In 1972 I purchased my own retail drugstore, Thayer's Colonial Pharmacy, Inc., located in Orlando, Florida. This drugstore had been in Orlando for many years with a reputation for finding unique prescription drugs and compounding various discontinued formulations. Included in this were many combinations of two or more drugs. For example, dermatological preparations and respiratory drugs were commonly compounded.

In the mid-1980's we began compounding various respiratory medications on a broader scale. This business grew rapidly, including a large portion of mail order transactions. We attracted much attention within the industry.

Around 1990, the FDA paid us a visit. Their mission was to investigate my compounding pharmacy. After 2 weeks of intense scrutiny, they determined that I should be "labeled" a manufacturer, and **ordered that I cease and desist this compounding** division of Thayer's. The FDA representatives said, "*If you want to be in the manufacturing business, then you must have an FDA-approved manufacturing facility*". Of course, the back room of my drug store did not qualify.

In 1991, following the FDA's instruction, I set out to secure the approvals and financing necessary to open a proper manufacturing facility. Although I was a bit naive at the outset, I soon learned that I was involved in a daunting process. In my case, it took over 6 years to secure approval for my first new drug product, and my plant. It was arduous, capital intensive and certainly the most challenging endeavor of my career in health care. However, I now understood the rules and knew this was necessary to begin providing prescription drugs on a large scale to the public. I knew this because the FDA had told me so.

In 1997 Nephron Pharmaceuticals was up and running as an FDA-approved and registered facility. Our focus is oral inhalation solutions used to treat asthma, bronchitis and Chronic Obstructive Pulmonary Disease. Nephron owns six approved Abbreviated New Drug Applications (ANDA's) for prescription drugs:

- Albuterol Sulfate Inh. Sol., 0.083 percent
- Albuterol Sulfate Inh. Sol., 0.5 percent
- Ipratropium Bromide Inh. Sol., 0.02 percent
- Isoetharine Inh. Sol., 1 percent
- Metaproterenol Sulfate Inh. Sol., 0.4 percent
- Metaproterenol Sulfate Inh. Sol., 0.6 percent

Now, by national pharmaceutical standards, we are little guys. Even so, here is what is entailed in the manufacture of our drugs:

Our 76,000 square foot facility is designed for full FDA compliance. Our production room design houses controlled environment rooms, based on the 1997 ISPE Sterile Manufacturing Facilities Guideline that was developed with the help of the FDA.

- Main Room classified as "Pharmaceutical" "D Grade", Class 100,000 in operation;
- Gown Room, Class 100,000
- Mix Room, Class 10,000
- Filling Room, Class 10,000 with Class 100 HEPA Shrouded fill nozzle systems
- All rooms use positive pressure, cascading air filtration systems.

The attached exhibits show the design of this facility (Attachment #1), the structured materials flow chart (Attachment #2), the complex HVAC system required (Attachments #3 and #4), and one of the Water for Injection systems required for operation (Attachment #5).

In this facility we have the following Departments/Personnel required to comply with drug manufacturing regulations (21 CFR § 210/211)

- Regulatory Department: **4 people** responsible for all **FDA compliance**/reporting

• Quality Assurance Department: **41 people** involved in document control, validation, training, batch record review and production line control;

• Quality Control: **9 degreed chemists**/technicians to analyze all active and inactive ingredients and finished product stability studies; **19 degreed microbiologists**/technicians who do environmental monitoring of all clean room, samples of WFI and Pure Steam condensate, sampling of raw materials and production components;

• Production Department: **117 production personnel**;

• Engineering Department: **4 Blow/Fill/Seal specialists** whose technology requires no human contact with the product or its immediate container during filling and is recognized by the US Pharmacopoeia (USP) as an advanced technology for the manufacture of liquid solution in unit-dose forms; **22 production equipment assistants**.

And these personnel operate at this facility in compliance with Federal Regulations (21 CFR § 210/211), which requires the following:

• 517 Production Standard Operating Procedures (SOP's);
• 30 Microbiology SOPs;
• 47 Chemistry SOPs;
• 29 Microbiology Validated Test Methods;
• 20 Chemistry Validated Test Methods;
• 219 Equipment Installation/Operation Qualification Procedures;
• 310 Performance Qualifications/Validated Processes.

As you can see, this is a highly complex industry. The FDA requirements, which are incredibly demanding, seem never-ending. However, as a manufacturer, I have the comfort of knowing that all FDA-approved facilities are subject to the same sets of regulations and requirements. These rules are not frivolous; they are there for a purpose. And that is to protect the public by insuring a uniform standard of integrity in the prescription drugs produced in our country.

Let me give you an example. We have to test the raw ingredients used in the manufacture of a batch of drugs at the beginning of the batch and at the end of the batch. If the composition of the raw ingredients does not meet their predefined specifications at the end of the batch, all the drugs in that batch MUST BE DESTROYED.

And yet, while these high standards are uniform with the FDA facilities, there is another sphere of drugs, in my case, inhalation drugs, which are produced throughout the country today with no similar level of accountability. Pharmacies, like Thayers, are producing drugs that should be identical to those produced by my company, but fall far short.

I have attached four reports (Attachments #6 to #9), of pharmacy-produced products sent to my chemistry lab at Nephron for analysis. As you can see, they miss the mark on potency and quantity. A recent study by the FDA itself showed a failure rate of more than 34 percent. These failures result from inadequate facilities as well as inadequate testing of raw ingredients.

Perhaps to attack this problem, the FDA instituted a rule that **all** *oral inhalation drugs have to be* **sterile**. Initially, receipt of this ruling reconfirmed to me that I had made the correct decision in 1991 to pursue FDA certification. However, in my trips around the country marketing my products, I encounter time after time non-FDA approved companies in the inhalation drug market willfully mass compounding their products. Let me assure you, their product is rampant. I know. I ran a similar operation in the 80's. I can tell you there is no comparison to the way I produced Albuterol in the back room at Thayers to the way Albuterol is now produced at Nephron.

Which brings us to the importance of the hearing you are holding today. Americans across the country believe that the drugs they purchase to fill a doctors prescription are the same . . . the same chemistry, the same sterility, the same integrity. This is certainly the ideal toward which the FDA and its registered manufacturers work. However, this is far from the reality. The consumer is at risk and does not even know it. The consumers do not know how to protect themselves from non-FDA drugs, or that they even do.

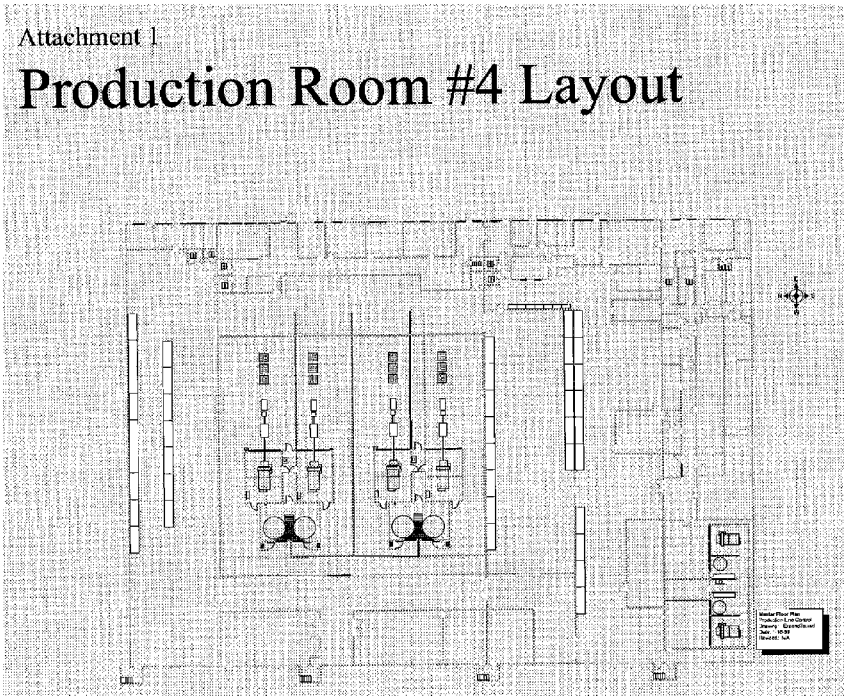
Clearly, the integrity of the prescription drug market in this country is under siege. Companies and individuals are willfully breaking the rules and regulations long established by the FDA. Given my background, and I find this situation is stunning. The consumer, however, should find it frightening. As you know from documented press stories, the result of this mass compounding outside the FDA arena can be lethal.

Again, thank you for providing this public forum to discuss this crisis. I am confident that with your attention, the double standard prevalent in the inhalation

drug market will no longer be tolerated. I would be happy to answer any questions you might have.

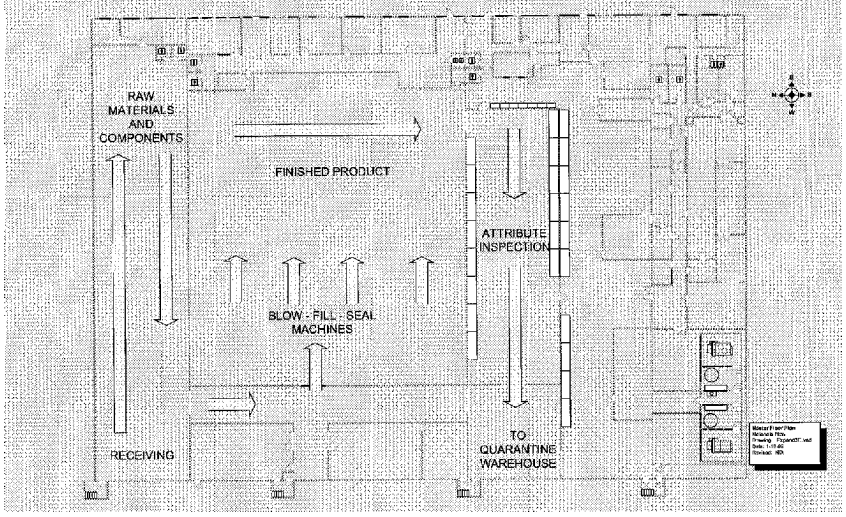
Attachment 1

Production Room #4 Layout



Attachment 2

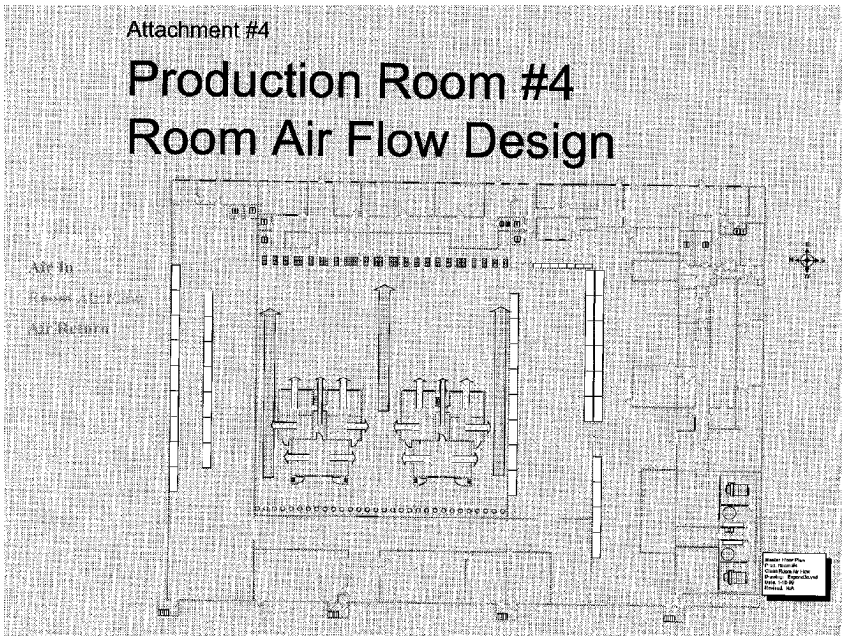
Production Room #4
Materials Flow

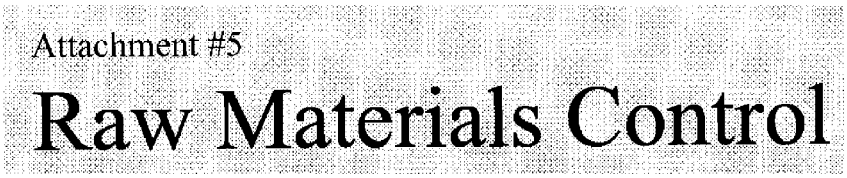


Attachment #3

Production Room #4

- HVAC
  - Primary Filtration
    - FAR 30/30 prefilters
    - 90/95 ASHRAE rated filters
    - 3 air handlers @ 29,000 cfm each
    - Approximately 23 room air changes per hour
  - Secondary Filtration
    - 68 HEPA filters @ 720 cfm each
    - Air supply = 87,270 cfm





PREPARED STATEMENT OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, ASHP

The American Society of Health-System Pharmacists (ASHP) is pleased to submit this statement for the record of the Senate Health, Education, Labor, and Pensions Committee hearing on pharmacy compounding. ASHP is the 30,000-member national professional association that represents pharmacists who practice in hospitals, long-term care facilities, home care, hospice, health maintenance organizations, and other components of health care systems.

ASHP is as concerned as this committee about inappropriate and fraudulent behaviors that have placed patients at risk of harm from their medications. One must distinguish however, between an intentional criminal act and pharmacy compounding.

ASHP has a long history of promoting safe medication use and has developed practice standards for pharmacy compounding in hospitals and other components of health systems. We foster the application of those standards through various articles published in our peer-reviewed, professional practice journal, and through educational sessions featured at our clinical meetings.

In an effort to help assure patients receive safe and appropriate medications, ASHP recognizes the need to collect additional information about all medication distribution systems, including compounded preparations. It is important to fit this examination into the proper regulatory framework.

ASHP strongly supports the current regulatory system, with State boards of pharmacy regulating pharmacy compounding and the FDA regulating the manufacturing of drug products. This regulatory framework is consistent with the way other health professions are regulated and is effective.

Throughout this testimony we will look at the nature and extent of pharmacy compounding and the system for regulating this practice. We will also examine ways to continue to improve the safety of the medication system.

ORIGINS OF THIS HEARING NOT COMPOUNDING

It is important to note that the origins of this hearing stem not from the practice of compounding as described below, but rather from the fraudulent and criminal acts of a Kansas City pharmacist who intentionally diluted the potency of chemotherapy drugs for his own economic gain. This pharmacist's actions were inexcusable, indefensible, and an embarrassment to the profession. His actions are not representative of the necessary, accurate, and admirable compounding that pharmacists perform everyday for patients in hospitals and health systems.

As the committee assesses the adequacy of current regulatory framework, it must not overlook this fact. The current justice and regulatory system is well-designed to deal with criminal action.

PHARMACY COMPOUNDING TODAY

The practice of compounding is an important and long-standing component of the pharmacy profession. In the early days of medicine, compounding frequently occurred because there were few commercially available products. Today, compounding allows pharmacists to customize manufactured products to meet individual patient needs or to create necessary alternatives to commercially available products.

Compounding occurs when a medication is prepared by combining, mixing, or altering two or more ingredients, or components, for a patient based on the receipt of a valid prescription or in anticipation of prescriptions based on the medication order history from the pharmacist-physician-patient relationship.

Pharmacists in health system settings generally prefer not to compound if there is a viable product commercially available, since compounding requires extra time, staff training, proper equipment, and other important quality control measures. However, proper patient care requires the compounding of certain medications. In fact, in hospitals, many commercially available products require compounding processes to prepare them for administration.

It is impossible for manufacturers to meet every conceivable patient need. For example, the variety of doses needed for geriatric and pediatric patient populations or the customization of intravenous fluids needed to correct a given patient's blood-chemistry deficiencies.

Further, manufacturers cannot manufacture certain items. The classic example of this is a sterile fluid for intravenous feeding of patients ("parenteral nutrition"). While manufacturers covet this large potential market, they have not been able to manufacture a stable product. The moment the necessary concentration of glucose and protein are mixed together, the ingredients begin to decompose. Parenteral nutrition has been an established therapy for 35 years, but manufacturers have not been able to resolve this chemical stability problem and provide a usable product to the health systems caring for these patients. Hence, pharmacists (for example in hospitals and home care) must do the compounding. For many patients, this is literally life-saving therapy.

Medications are also compounded when a prescriber determines, in his or her professional judgment, that the use of a compounded preparation is necessary. For example, when a patient cannot use a commercially available product due to an allergy to one of the ingredients—sensitivity to the dye used for coloring, lactose, or other excipients used in many classes of drugs. Or, when a patient cannot swallow tablets or capsules and the drug can be transformed into a liquid, lozenge, suppository, or other form.

The compounding of medications that would not have been otherwise available has saved many lives. This is thanks to the dedication, skill, and professional judgment of pharmacists. It is clearly within the public interest to preserve this important practice.

REGULATORY OVERSIGHT OF PHARMACY COMPOUNDING IS WELL ESTABLISHED

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) was created to regulate drug manufacturing, marketing, and distribution, not compounding or pharmacy practice. The Food and Drug Administration Modernization Act of 1997 (FDAMA), which ASHP worked with Congress to develop, reinforced the legitimacy of pharmacy compounding as a State regulated activity and clarified the inapplicability of the FDCA to compounding. Although the compounding provision of FDAMA

was overturned by the Supreme Court in 2002 due to its constraints on advertising, this should not eliminate the line between Federal and State jurisdiction.

The oversight of pharmacy practice by State regulatory authorities is well established. States, through their boards of pharmacy, determine the education and licensure requirements of pharmacists, as well as licensure requirements for pharmacies. State boards of pharmacy have the authority to take disciplinary action, including license revocation or suspension, against pharmacists for misconduct or failure to abide by State laws or regulations, including those pertaining to pharmacy compounding. This is equivalent to the way physicians and other health care professionals are regulated.

The role of enforcing the application of specific quality assurance standards in pharmacy practice is one that is well established in law and in practice for State boards of pharmacy. The FDA recognized this in its December 28, 1998, draft "Memorandum of Understanding on Interstate Distribution of Compounded Drug Products." In that document the agency states that "the standard MOU also reflects FDA's policy to defer to State and local officials for the regulation of the day-to-day practice of pharmacy, to the extent permitted under the Federal Food Drug and Cosmetic Act."

The State boards of pharmacy are admittedly at different stages in their efforts to regulate compounding practice, with some States aggressively addressing good compounding practice. California, for example, has adopted regulations establishing standards for compounding injectable preparations, requiring special licenses for those who prepare sterile formulations, and increasing investigation of compounding pharmacies.

Other States may need to continue to strengthen their regulatory authority of pharmacy compounding. Over the past few years, public awareness of pharmacy compounding has grown and many States are in the process of addressing the issue. The National Association of Boards of Pharmacy (NABP), in a continued effort to provide guidance to the States, has strengthened its model practice act on compounding.

The United States Pharmacopeia (USP) has also promulgated a revised chapter on the compounding of sterile products, known as General Tests and Assays Chapter 797 or "Pharmaceutical Compounding—Sterile Preparation." Beginning January l, 2004, this chapter could be enforced by State boards of pharmacy if adopted by State statute or regulation and cited during visits by FDA and accreditation personnel. This chapter provides a standard for sterile compounding. The USP also provides a similar standard on non-sterile compounding.

BUILD UPON THE CURRENT FEDERAL—STATE PARTNERSHIP

Much can be done to build upon the existing Federal—State partnership to ensure patient safety. For example, ASHP strongly supports the development and widespread distribution of minimum standards and appropriate guidance for pharmacists and others on pharmacy compounding. While ASHP believes State boards of pharmacy are the appropriate body to enforce compounding standards, the FDA has a role to play in ensuring that the State boards fulfill this responsibility through the State adoption of uniform standards. ASHP believes that it is appropriate for the FDA to suggest to State boards the standards that the States should apply. This will foster the establishment of a national quality assurance standard for compounding in all pharmacy settings, rather than 50 different standards. The use of both the USP chapters and ASHP guidelines on sterile and non-sterile compounding, as well as the latest scientific knowledge in the literature, would provide the assurance the committee is seeking for the safety and effectiveness of these preparations.

The FDA could also play an important role in bolstering State enforcement efforts. State boards have limited resources to hire inspectors and to train them properly. The FDA could offer a training program for State inspectors enforcing the minimum national standards for compounding practice. This could be run similar to the Federal program whereby States receive dollars to help maintain their roads when the State chooses to enforce the 65 mile per hour speed limit. The FDA should also have clear procedures for State inspectors to call in the FDA when activities seem to border on manufacturing.

Finally, it would be beneficial if there was more clarity and consistency in the definitions of compounding and manufacturing. When section 127 of FDAMA was overturned, this became less clear. In the policy compliance guide on pharmacy compounding issued by the FDA in June 2002, the FDA identified nine factors that it would use collectively to determine when the scope and nature of activities raise the kinds of concerns normally associated with drug manufacturing. In the FDA's

revision of the compliance policy guide, it may be helpful if the FDA provides a definition of what actually constitutes manufacturing rather than just providing examples of what oversteps the bounds of "traditional pharmacy compounding." The USP in its draft chapter 1075, "Good Compounding Practice," also provides a definition for compounding and manufacturing. The FDA and USP should be encouraged to coordinate finalization of their respective compliance guides and chapters so that their definitions and criteria for compounding and manufacturing are consistent.

CONCLUSION

The existing Federal—State partnership provides a good framework for regulating medication distribution, including compounded preparations. This committee should build on the existing framework in the ways suggested above rather than adding additional Federal regulatory oversight.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS (IACP),
SUGAR LAND, TEXAS 77487,
October 23, 2003.

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
U.S. Senate,
Washington, DC 20510.

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE: The International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to present this written discussion of pharmacy compounding. IACP's mission includes increasing awareness of the importance of compounding by providing accurate information. on the benefits of compounding and providing assistance to pharmacists in improving their compounding practices. In this capacity, IACP wishes to address a number of issues relevant to this hearing. IACP submits these comments on behalf of its 1,800 member compounding pharmacists and their pall patients, who benefit from compounded medications.

The Importance of Compounding

Compounding of medication for patient use has been a fundamental component of pharmacy practice and healthcare since ancient times. Compounding is the origin of the practice of pharmacy and has continued to be a vital element of healthcare throughout the evolution of pharmacy and medicine.

Pharmacy compounding is traditionally characterized by a physician/pharmacist/patient relationship, in which professionals work, together to customize or individualize medications for a patient. Compounding is performed under the supervision of a pharmacist, who is trained in the unique knowledge and skill required for compounding during pharmacy education and is subsequently licensed by State Boards of Pharmacy.

Compounding is defined by the National Association Boards of Pharmacy (NABP) Model Pharmacy Act as:

Compounding—The preparation, mixing, assembling, packaging, or labeling of a drug or device (I) as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice or (ii) for the purpose of, as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed prescribing patterns.

Every State authorizes pharmacists to compound.

Compounding may involve a variety of different activities in different practice settings. Examples of compounding activities include the preparation of oral liquids, topical ointments, and suppositories; the conversion of one dosage form into another; the flavoring of medication to make the medication palatable for a patient; and the preparation of pediatric dosage forms from adult dosage forms.

Physicians and pharmacists recognize that some individual healthcare needs cannot be met by commercially available, manufactured, mass-produced drug products, produced in limited formulations and strengths. Many patients need customized medications to address specific medical problems. Manufacturers are unable to tailor-make a customized medication for a single patient or a small group of patients in an efficient and cost effective manner. Without compounding in these cases, patients would be forced to forego their medications or to substitute a product that may not meet their medical heeds.Compounding pharmacists work in their communities, alongside the physicians who write prescriptions for compounded medications, as problem solvers to meet these unique needs.

Compounding provides life-saving therapy to many classes of patients who would otherwise be unable to obtain necessary medications. Pediatric or geriatric patients

may need extremely small dosages. The American Pharmacists Association (APhA) has reported an. estimate that more than 40 percent of doses given in pediatric hospitals require compounding to prepare a suitable dosage form. Further, compounding pharmacists provide therapy for many hospice patients nearing the end of their lives, who can no longer benefit from curative treatment and generally have a life expectancy of six (6) months or less. Many of these patients can no longer swallow their pills; for others, commercial doses are inadequate. Compounding pharmacists help to develop drug therapy programs that minimize pain and symptoms for hospice patients and work to enhance the quality of life for hospice patients in their final days. In addition, patients may be allergic to specific ingredients in a commercially available product. Compounding pharmacists can work with physicians to alleviate this problem by omitting the problematic ingredient in a formulation or by customizing a similar medication to meet the patient's need.

In sum, compounding is a critical component of pharmacy and healthcare. Indeed, just last year the U.S. Supreme Court, in the Thompson v. Western States Medical Center case, acknowledged the importance of compounding.

How Does Compounding Differ From Manufacturing?

The NABP Model Pharmacy Act defines manufacturing as:

Manufacturing—The production, preparation, propagation, conversion or processing of a Drug or Device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or Labeling or relabeling of its container, and the promotion and marketing of such Drugs or Devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compound for resale by pharmacies, Practitioners, or other Persons.

The fundamental difference between compounding and manufacturing is the presence of a physcian/pharmacist/patient relationship, which controls the preparation and distribution of a compounded drug medication. Pharmacy compounding is performed at the pharmacy site for nearly immediate dispensing or administration to the patient. Compounded medications are not offered for resale, but instead are customized to meet a patient's specific medical needs. The profession's definition of compounding does not encompass the preparation of massive amounts of a drug product with the purpose of distribution to a mass market of unknown users in unknown venues. Instead, the pharmacist directly interacts with the patient and is available to advise patients on characteristics and use of a compounded medication. Pharmacists, unlike drug manufacturers, offer counseling to patients. Based on this relationship between pharmacist and patient, a pharmacist may often monitor a patient's reaction to a compounded medication and advises patients to immediately report adverse reactions.

This relationship between the compounding pharmacist and the practitioner provides an appropriate system of checks and balances to ensure that the patient's health is protected and served. A legally compounded medication by a pharmacist is authorized by a prescription from a physician. The pharmacist acts as a valuable resource for determining the customized elements of a compounded medication such as dosage formulation, drug compatibility, etc., to meet the patient's needs and to facilitate prescribe-intended outcomes. The pharmacist may also refuse to dispense a prescription that requires compounding of a drug which is not appropriate for that patient or cannot be compounded. The relationship between physician, pharmacist, and patient likewise provides an appropriate level of checks and balances to ensure patient care.

Manufacturing, on the other hand, involves the production of batches of drug products consisting of millions of dosage units, such as tablets or capsules, for resale. Manufactured products are distributed through the normal chains of interstate commerce to individuals unknown to the company. Manufacturers are not required to, and do not, monitor individual patients' response to medications or answer patient questions.

The Robert Courtney Case

It is important to note that reconstitution, the pharmacy practice engaged in by Robert Courtney, is a practice that is generally not considered to be compounding. The oversight actions initiated by Senators Bond and Roberts, including this hearing, stem from understandable concerns about the criminal activity and professional misconduct of Robert Courtney, a former pharmacist in Kansas City, MO. Courtney intentionally diluted the potency of cancer drugs over a sustained period of time for profit and, as a result of these criminal activities, has been convicted and imprisoned. IACP condemns the actions of Courtney. However, we strongly believe that

Courtney's actions cannot be extrapolated to represent the profession of pharmacy in general, or more importantly, compounding pharmacy, While Courtney's actions were reprehensible, it is important to note that his actions were the actions of one individual and should not be used to judge the thousands of pharmacists that practice in this country. Pharmacists are highly committed to the care of their patients and compliance with high professional and ethical standards. The Courtney case should not prompt Congress to challenge the integrity or oversight of the profession of pharmacy.

Reconstitution of a commercial product according to the manufacturer's FDA-approved instructions, a routine practice virtually every hospital *and the action performed by pharmacist Robert Courtney in preparing chemotherapy products, is not considered to be "compounding*." Congress, in the Food and Drug Administration Modernization Act of 1997 (FDAMA), specifically exempted from its definition of compounding "reconstituting . . . that [is] performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling." Further, the FDA's current approach to oversight of compounding practices, its Pharmacy Compounding Compliance Policy Guide (CPG), does not address reconstitution. According to broadly accepted definitions, Robert Courtney's criminal activities would not be identified as compounding. Courtney's illegal acts in no way provide justification for imposing new restrictions on compounding.

How is Compounding Regulated?

Since compounding is a traditional component of the practice of pharmacy, compounding is appropriately regulated by State Boards of Pharmacy. The State Boards of Pharmacy and standard-setting organizations such as the U.S. Pharmacopeia (USP) and the National Association of Boards of Pharmacy (NABP) have effectively regulated the practice of. compounding pharmacy for many years.

A majority of the State Boards of Pharmacy have regulations in place that specifically address compounding practices. In addition, many States have recently revised or are currently updating their compounding regulations. As part of its Model Pharmacy Act, NABP also has made model Good Compounding Practices (GCPs) available to State Boards of Pharmacy as a template for compounding regulations. Further, the United States Pharmacopeia has recently revised four guidance chapters on pharmacy compounding: Chapter 795, Pharmaceutical Compounding—Nonsterile Preparations; Chapter 797, Pharmacy Compounding—Sterile Preparations; Chapter 1075, Good Compounding Practices; and Chapter 1161, Pharmaceutical Calculations in Prescription Compounding.

In 1997, Congress addressed the practice of pharmacy compounding in the Food and Drug Administration Modernization Act (FDAMA). In this Act, Congress recognized compounding as a vital healthcare service that must be preserved, leaving the role of the State boards as its regulators intact. The subsequent decision by the Supreme Court to void the Act was premised on the lack of a severability clause and the unconstitutionality of constraints on commercial free speech. In view of the Court's decision, FDA is now in the process of refining its CPG, which would articulate its views on Federal jurisdiction.

The Roles of State and Federal Regulatory Bodies in Compounding and Manufacturing

Drug manufacturers are regulated, among other entities, by the U.S. Food and Drug Administration (FDA) under the authority of the Food, Drug, and Cosmetic Act of 1938 (FDCA). The provisions of the FDCA have been designed to prevent the production of ineffective or dangerous manufactured drugs and their introduction into commerce.

The FDCA and the processes it requires were designed to address situations where a drug product would be developed, approved as to its safety and efficacy, marketed throughout the United States, and ultimately dispensed to patients with whom the manufacturer has had no contact. There is an obvious distinction between a manufactured drug and a compounded medication. A compounded medication is one that is formulated for a specific patient need, such as an allergy to an ingredient, that cannot be met by a mass manufactured drug.

In short, FDA regulates manufacturing of medications, while State Boards of Pharmacy regulate pharmacy practices, including the compounding of medications. FDA should work with State Boards of Pharmacy and pharmacy organizations to develop the distinction between pharmacy compounding and manufacturing. However, compounding pharmacists must not be subject to regulation by FDA under the FDCA and must, instead, remain within the regulatory control of State Boards of

Pharmacy. There has been no evidence shown to support federalization of pharmacy oversight.

Quality Assurance for Compounded Medications

The quality of compounded medications can be assured through adequate State and self-regulation of compounding practices, training and other mechanisms. While there have been some compounding pharmacies that have had significant quality problems they represent a small minority. The overwhelming majority of compounded medications meet these quality standards. Nevertheless, IACP and the pharmacy profession arc committed to improving quality and training.

Initially, we must assist State Boards of Pharmacy in assuring that they have regulations that address the practice of compounding. Most States already have regulations in place or are in the process of developing regulations. However, we must assist the few Boards of Pharmacy that do not have regulations for pharmacy compounding in either adopting the NABP Good Compounding Practices (GCPs) or in crafting their own regulations. Further, we must ensure that State Boards of Pharmacy have the funding required to monitor compounding practices in their States and to enforce compounding regulations. Providing necessary resources and fiscal support to State Boards of Pharmacy is essential for assuring the quality of compounded medications.

In addition, the United States Pharmacopeia has developed guidelines that help to ensure the quality of compounding medications. Pharmacists' knowledge of and adherence to the guidelines will result in continuous quality improvement of compounded preparations.

Personnel education is also an essential factor in compounded medication quality. In recent years, there has been tremendous growth in the availability of American Council of Pharmaceutical Education (ACPE) accredited education programming related to quality compounding pharmacy practice. We must work together to increase and enhance such programs.

Finally, IACP is currently leading efforts to develop profession-driven, comprehensive standards of practice for compounding with the goal of educating compounding pharmacists on best practices and processes that can be used to ensure quality compounded medications for patients. We are also developing an accreditation program for pharmacies where compounding occurs. Such an accreditation program would assess and improve compliance to standards of practice.

These combined factors will effectively address the quality of compounded medications.

IACP appreciates the opportunity to share this testimony with the Senate HELP Committee. If we can be of any assistance, or if you have any questions, please do not hesitate to contact me at (281) 933–8400.

Respectfully submitted,

L.D. KING,
IACP Executive Director.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS,
SUGAR LAND, TX 77487,
October 30, 2003.

Hon. JUDD GREGG,
Chairman,
Committee on Health, Education, Labor and Pensions ,
U.S. Senate,
Washington, DC 20510.

DEAR CHAIRMAN GREGG: During the Thursday, October 23 hearing, "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients," hearing chairman Senator Kit Bond indicated his intent to keep the record open to receive supplemental remarks. The International Academy of Compounding Pharmacists (IACP) would greatly appreciate your incorporating the following into the hearing record.

Mr. Chairman, you are likely to have been aware of our concerns about the witnesses invited to testify and the committee's need to receive a balanced viewpoint. Several witnesses were predictably hostile toward compounding; however, most notable were the comments of others. The General Accounting Office (GAO) observed ongoing efforts at the State-level (through State boards of pharmacy) and national-level (through professional organizations) that should provide confidence to the committee that significant steps are underway to strengthen oversight of compounding. The Food and Drug Administration, while chastised for its use of a limited survey

to convey anecdotal information critical of compounding, nonetheless acknowledged continued deference to the States' enforcement. While we may disagree on some of the specific statements they made, we are heartened by both agencies' acknowledgement of the unique and beneficial role that pharmacy compounding plays in the Nation's health care.

Three areas of discussion at the hearing, however, require IACP's supplemental comments:

1. Reference was made to a provision in pending Medicare drug benefit legislation that would create an advisory committee at FDA to examine pharmacy compounding. We continue to oppose this provision and note that the hearing produced little evidence to alter this perspective. If anything, acknowledgement of the predominant States' role and efforts underway to improve regulation at the State level call for continued deference to the States and not, as the amendment suggests, imposition of Federal authority over what has been the States' task. As the GAO pointed out, a number of States also have new initiatives to tighten regulations. The examples cited by the GAO are not unique, for example, California recently implemented new regulations and Texas is in the process of adopting new regulations. Further, IACP believes that the advisory committee is an inefficient use of FDA resources and energies, particularly when there has been little justification for Federal intervention. This is particularly true at a time when FDA needs to expend its resources regulating illegal internet pharmacies and drug diversions. FDA should not divert its resources to pharmacy practices that are already licensed and regulated by the States.

2. IACP asks the committee to take note of the relatively limited number of adverse events (GAO estimates 200 over the past several years) compared to the 30 million estimated compounded prescriptions dispensed each year. While we are concerned about the adverse events that have occurred and are taking steps to prevent future occurrences, it is also important to note that compounding pharmacy has a strong overall safety record. All observers have acknowledged the paucity of hard data relating to compounding. Regulatory bodies (State or Federal) would have to redirect energies and resources at a "problem" where no analytic data exists to show a troubling incidence of unreported events. While we believe compounding can be improved, and we are working toward that goal, the low incidents of adverse events do not justify requiring a new reporting system.

IACP believes that adverse event reporting is better accomplished by the national professional organizations who have an ability to assess information and then develop informational and educational resources to address any problematic trends that are identified. IACP would direct your attention to a voluntary reporting system established by U.S. Pharmacopeia (USP) in the 1990s—"MedMaRX." This adverse reporting mechanism exists today, although it would require greater visibility and participation by professional pharmacists. IACP views this or a comparable system developed by national professional organizations as a credible alternative. We hasten to add that any system must be voluntary, primarily because it is critical for pharmacists, physicians, and patients first to assess whether an adverse event has in fact occurred. The routine, mandatory and uncritical reporting of all possible such events will inundate the system, which will become so overloaded with raw data that it would have little practical value.

Further, capturing adverse events is an issue that the entire pharmaceutical industry is working to address. It is commonly understood throughout all of healthcare that we must do a better job of capturing data related to adverse events. Likewise, compounding pharmacy practice is not unique in this venue.

3. Several Senators and witnesses commented on whether there is a lack of clarity on FDA's regulatory authority. For example, some asked if there should be a "bright line" separating compounding from manufacturing. Also, others noted areas within the Compliance Policy Guide (CPG) that are seen as overly vague.

IACP believes that there is a process within FDA that is entirely appropriate to resolve these criticisms. Let us note for the record that IACP has been a stern critic of the current CPG. We have sought substantial change. We are, however, willing to let this process continue. At the hearing, FDA committed to responding to the comments it had received. We believe that FDA's internal review process should be completed before Federal legislation is contemplated.

Mr. Chairman, IACP greatly appreciates your consideration of our views. We look forward to working with you constructively in developing the appropriate balance between Federal and State jurisdiction.

Sincerely,

L.D. KING,
IACP Executive Director.

PREPARED STATEMENT OF THE AMERICAN PHARMACISTS ASSOCIATION

Good morning. Thank you for the opportunity to appear before you today and present the views of the American Pharmacists Association. I am Dan Herbert, a pharmacist and the President-elect of APhA. I have been in practice for 37 years and currently own three community pharmacies in Richmond, Virginia. Founded in 1852 as the American Pharmaceutical Association, we are the largest national pharmacist organization in the United States, representing more than 53,000 practicing pharmacists, pharmaceutical scientists, student pharmacists and pharmacy technicians. APhA members practice in virtually every area of pharmacy practice, including independent and chain community pharmacy, hospital pharmacy, nuclear pharmacy, long term care pharmacy, home health care and hospice.

Let me first provide APhA's support of the committee's goal that patients receive safe and effective medications. As pharmacists, we rely upon quality products as the first step in our work to help patients make the best use of their medications. When providing a quality product involves tailoring a medication for an individual patient, we use our scientific training and education to compound the medication.

Compounding medications is an important component of pharmacy practice—mine and that of my colleagues. While it is challenging to quantify the actual number of APhA's members who engage in drug compounding activities on a regular basis, virtually all practicing pharmacists will be involved with compounding activities at some point during their career—and most practitioners engage in some element of compounding in each week of practice. APhA has a compelling interest in helping pharmacists, in collaboration with practicing physicians, compound drug formulations to meet the needs of patients. Our compounding activities are a critical component of the American health care system, allowing physicians to prescribe medication therapy to best meet the needs of their patients.

My comments today will provide a brief history of pharmacist compounding, a description of the important role it plays in our health care system, the challenging task of distinguishing between compounding and manufacturing, and ways in which we can attempt to appropriately protect our patients by improving the quality of practice and identifying and stopping "bad actors".

Compounding: A Traditional Component of Pharmacy Practice

Compounding is a traditional component of pharmacy practice; only the drugs, dosage forms, and equipment or techniques have changed as pharmacy practice has advanced. As noted in the *Chronicles of Pharmacy*, "[p]harmacy, or the art of selecting, extracting, preparing and compounding medicines from vegetable, animal, and mineral substances, is an acquirement that must have been almost as ancient as man himself on earth." The early practice of pharmacy required the compounding of virtually all medications, because there were few, if any, commercially available products. The need for compounded products has diminished with the founding of pharmaceutical companies, although the need for this practice still exists today. Because the preparation of an extemporaneous pharmaceutical dosage form is not a trivial exercise, our position is that when an FDA-approved, commercially available product can meet a patient's needs, it should be employed as the preferred course of action. However, when a patient's particular situation obviates the use of commercial products, the knowledge and skills of a compounding pharmacist can be extremely valuable, even lifesaving.

It is a fundamental responsibility of the pharmacy profession to extemporaneously compound quality prescription products for patients who have unique medication needs. Through their education and licensure, pharmacists assume an ethical obligation to the public to maximize the intended benefits of drug therapy while minimizing the unintended side effects and adverse reactions. Some Sates require licensed pharmacies to offer compounding services [see 49 Pa. Code § 27.18(p)(2) (2003);W. Va. Code St. R. § 15-1-19.4 (2003)]. Compounding enables pharmacists to use their knowledge and expertise of medication use to produce individualized medications that meet patient needs and improve health outcomes. Without compounding, pharmacists and physicians would be limited to a "one size fits all" strategy, which would have a direct, immediate, negative impact on the ability of health care providers to provide care to patients.

Compounding Necessary for Many Patients

As I stated earlier, it is challenging to quantify the actual number of pharmacists who engage in drug compounding activities on a regular basis, virtually all practicing pharmacists will be involved with compounding activities at some point. The unique knowledge and skill set of pharmacists enables them to extemporaneously compound medications to individualize patient care through the preparation of patient-specific products.

Compounding allows pharmacists and physicians to address the health care needs of patients who do not fall within the range of commercially available dosage strength and formulations. Patient needs vary from extremely small doses and specific combinations of drugs, to preservative-free products, to liquid dosage forms, to delivery systems that are not commercially available. In many situations, large-scale manufacturers are unable to tailor-make a medication in a cost effective manner. Without compounding, many patients would not have access to the correct combination of ingredients, the appropriate dose and dosage form, or the best delivery system.

In addition to unique patient needs, manufacturing and market limitations may require medications to be compounded. For example, some therapies, such as hyaluronidase injection (used as an adjunct to ophthalmologic surgery) must be compounded because the therapies generate insufficient revenue to pharmaceutical companies to justify large-scale manufacturing. Other medications, such as radioactive drugs used to diagnose or treat cancers or other diseases, must be compounded because they do not have sufficient "shelf life" to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. And finally, many manufactured "finished pharmaceutical" products are only "finished" in the sense of being ready to ship and then store in the pharmacy. These products must still be compounded, or in some cases merely reconstituted, by the pharmacist to provide a dosage form suitable for a patient's treatment.

Compounding involves different activities in different pharmacy practice settings. It may mean the preparation of oral liquids, topicals, or suppositories; the conversion of one dose or dosage form into another; the preparation of specific dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, or pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting. Examples of some of the most common compounded products include lotions, ointments, creams, gels, suppositories, intravenously administered fluids and medications, total parenteral nutrition products, and oral suspensions.

Although compounding may be required in any pharmacy practice setting and for any type of disease, there are concentrations of compounding practice. For example, due to the nature of the care they provide, hospital pharmacies have historically had a strong compounding component to their practice. And due to the nature of the disease and/or the patient size or age, compounding frequently occurs for patients with cancer, for pediatric care, and for hospice care.

Compounding in the hospital setting is a vital service that addresses the unique needs of patients requiring highly individualized medications. The primary compounding activity in hospitals is the preparation of intravenous admixtures ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens. Because daily intravenous therapy is provided through compounding of medications, nearly every person who has ever been admitted to a hospital—and those who will be admitted today and likely in the future—has received a compounded medication. In fact, the immediate availability of extemporaneous compounding by a pharmacist provides the hospital physician with literally any form or strength of medication needed for a patient's specific needs.

Cancer patients frequently benefit from compounding pharmacists' knowledge and skills. Almost all chemotherapy involves drugs and drug combinations that are compounded, or at least reconstituted, by pharmacists. It is imperative that a patient receive the correct drug dosage based upon the patient's body size, the type of cancer, the size and type of tumor, and the clinical condition of the patient including their kidney and liver function. This can often only be accomplished by using compounded, patient-specific medication preparations.

The compounding of pediatric dosage forms has also been an area of extensive activity, because many drugs used to treat children are only available in adult dosage forms. As the committee is aware, finding the right drug, dose and dosage form to treat sick children is a complicated task. This committee has made great strides in establishing incentives to improve the utility of manufactured products in treating children, but frequently, compounding is the only available avenue to achieve the desired clinical outcomes. Commercially manufactured products for adult use must be modified and compounded for use in children. It has been estimated that more than 40 percent of doses given in pediatric hospitals require compounding to prepare a suitable dosage form. Indeed, utilization of compounded medications is essential for the provision of medical care to hospitalized children.

As the committee is aware, hospice programs provide care for patients near the end of their lives who can no longer benefit from curative treatment and generally have a life expectancy of 6 months or less. Patients suffering from incurable cancer

have very special needs. Relief of pain near the end of life is an important element of maintaining the dignity and comfort of a dying patient and their loved ones. Hospice pharmacists often use compounded medications to alleviate pain and to control nausea and vomiting for patients in the hospice setting. A problem for many hospice patients is that pain medications are not manufactured in the required dosages. If commercial products that provide the precise dose(s) required are not available, the hospice pharmacist can often remedy the situation by extemporaneously preparing an individualized product. Additionally, some patients are not physically capable of swallowing the number of commercially manufactured tablets or capsules required or cannot take medications orally. A pharmacist can address these issues by either compounding a stronger product, by transforming tablets or capsules into a liquid, or by creating a preparation that can be applied topically or delivered rectally.

Continuous Quality Improvement

Pharmacy compounding conforming to the highest possible professional standards is essential to optimal patient care. But maintaining quality and advancing practice requires the profession to be vigilant, and continually improve our professional standards and regulatory efforts. One question that continues to plague the profession and our regulators—the State boards of pharmacy—is how to distinguish between compounding and manufacturing; with one practice regulated by State boards of pharmacy and the other process, by the Food and Drug Administration.

Compounding has traditionally been characterized by the triad relationship of the physician, pharmacist and patient; working together to individualize care for maximum patient benefit. Pharmacy compounding is performed in response to a prescription from a licensed prescriber, or in preparation for a reasonably anticipated prescription, based upon prior experience and expected needs of individual patients.

APhA supports the National Association of Boards of Pharmacy's (NABP) definition of compounding, which states:

Compounding—The preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice or (ii) for the purpose of, as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed patterns. [emphasis added] *(Good Compounding Practices Applicable to State Licensed Pharmacies*, Subpart A. Park Ridge, IL:NABP, 1993.)

The profession's definition of compounding does not encompass the preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues. Rather, the definition supports our assertion that the purpose of pharmacist compounding is to prepare an individualized drug treatment for a patient based on an order from a duly licensed prescriber.

Manufacturing, on the other hand, is defined by NABP as follows:

Manufacturing—The production, preparation, propagation, conversion or processing of a Drug or Device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or Labeling or relabeling of its container, and the promotion and marketing of such Drugs or Devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compound for resale by pharmacies, Practitioners, or other Persons. (Id.)

As clear as this difference may seem to the profession of pharmacy, it has been a difficult distinction to implement because of the complexity and range of legitimate compounding activities. In public comments, even the Food and Drug Administration has suggested that the difference between compounding and manufacturing is better represented by the intersection of two jagged jigsaw puzzle pieces rather than a straight line.

The fundamental difference between compounding and manufacturing, and the key element in making any such distinction, is the existence of a pharmacist/prescriber/patient relationship. This triad should control the preparation of a drug product. Furthermore, compounded drugs are not for resale, but rather, are personal and responsive to a patient's immediate needs. Conversely, drug manufacturers produce batches consisting of millions of tablets or capsules at a time for resale, while utilizing many personnel and large scale manufacturing equipment, without knowledge of the specific patient who will ultimately consume them.

There are numerous factors to consider in distinguishing the FDA-regulated practice of manufacturing from the State-regulated practice of compounding. Such factors—though none is exclusive—include the volume of compounding by a particular

pharmacist or pharmacy, the number of different products being compounded, the scope of the pharmacist's and pharmacy's practice, and of course, the presence of individual prescriptions for each compounded product.

Ongoing Activities; Opportunities for the Future

As professionals, pharmacists continually strive to provide the best patient care possible, including continuous review of practices and taking steps to improve medication use and advance patient care. While some may assert that little is being done to advance and improve pharmacist compounding, they are mistaken. APhA publishes resources for pharmacists to improve the practice, including *The Art, Science and Technology of Pharmaceutical Compounding and Trissel's Stability of Compounded Formulations*. And I am currently chairing an APhA committee setting strategic directions for the profession—including compounding. In our year of meetings, we have proposed some steps for advancing compounding practice as part of our commitment to providing safe and effective pharmaceutical care to the citizens of this country.

One aspect of our committee's work to date is the preliminary categorization of compounding to distinguish the types of compounding a pharmacist should be prepared to provide based on our pharmacy education and training, from the types of compounding that may require enhanced education or perhaps accreditation or certification processes. Because compounding encompasses a broad scope of activities—from the preparation of rather simple lotions for application to the skin to the preparation of radiopharmaceuticals for injection imaging, this categorization is important in focusing quality improvement efforts and resources. Our committee is also considering a proposal that pharmacists identify all compounded products for patients, so that patients understand that they will be using a non-commercially available product prepared specifically for their needs.

Other groups are pursuing efforts to improve pharmacy compounding practice as well. The United States Pharmacopeia (USP), the official drug standard setting body for our country, has a long history of addressing pharmacy compounding, especially in the area of sterile preparations. Various State boards of pharmacy are exploring changes in statute and regulation to more clearly articulate the boundaries of practice for pharmacists in their jurisdiction. In my home State of Virginia, legislation passed in the 2003 session made changes to our compounding requirements. Specifically, the legislation clarified that compounded products be prepared and dispensed pursuant to a prescription and in the context of a bona fide practitioner-patient-pharmacist relationship; or in expectation of receiving a valid prescription based on observed prescribing patterns. All compounded products must be labeled and include a beyond-use date. In addition, a pharmacist is required to maintain and comply with a policy and procedure manual if their practice involves compounding products that are at high risk for contamination, radiopharmaceuticals, or dose-critical or specialized preparation dosages.

And APhA and other representatives of the profession of pharmacy are evaluating the issue and proposing solutions as well. In collaboration with the National Association of Boards of Pharmacy and the United States Pharmacopeia, our groups have recommended exploring the value of voluntary programs to improve compounding activity in certain categories. For example, should pharmacists engaged in compounding complex sterile products—such as those prepared from non-sterile bulk chemicals—have their pharmacy practice complete a site accreditation process to assess the policies and procedures employed? Should pharmacists engaged in other complex compounding activities complete specific training and education programs, or even an individual certification process to demonstrate their knowledge and skills? While this work is early in development, we are making progress and will continue our work to assure that patients get the compounded medications they need, at the level of quality they should expect.

Improving our efforts to provide quality compounded products will require collaborative efforts of consumers, the profession, State boards of pharmacy, and the FDA. Each stakeholder has an expertise that is essential in assuring the continued availability of this practice with the quality patients deserve. Consumers must play a role in all of our efforts, as we are pursuing this work for them. The profession must take the lead in guiding the regulatory agencies in how to draw the line between compounding and manufacturing, and in developing guidelines and voluntary accreditation or certification processes to demonstrate compliance with those guidelines. The State boards of pharmacy, responsible for regulating the profession, should maintain their primary regulatory role of pharmacy practice, including compounding, and will likely be tasked with new initiatives to enhance current regulatory efforts. The FDA has a role in regulating manufacturers, as well as defining some broad guidance, such as the identification of substances that should not be

used in manufacturing or compounding because the substances have been withdrawn from the market for safety and efficacy concerns. All of these efforts require collaboration, coordination, and ongoing communication.

Through compounding, pharmacists fulfill a legitimate and essential need —providing patients with medications tailored to their needs. The professional education and training of pharmacists provides the unique knowledge and skills necessary to fulfill this health care need. The profession continues to research the most stable and appropriate mechanisms to produce compounded products, utilizing available and emerging technologies. By working together, prescribers and pharmacists help patients access otherwise unavailable therapies such as cream for breast cancer patients' radiation burns, or anticonvulsants in a suppository form when patients' veins are not accessible for injection. Without compounding, many physicians, pharmacists and patients would lose access to valuable treatments.

APhA supports the committee's efforts to discuss this important issue. Pharmacist compounding improves patients' lives every day, but we must continually improve our practices to provide the best patient care. Pharmacists are ready to partner with stakeholders to develop effective strategies to improving the quality of compounding practices. APhA appreciates the opportunity to share the perspective of pharmacists on this issue.

[Whereupon, at 11:45 a.m., the committee adjourned.]

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