DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

MAR 07 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the May 23, 2013, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Examining Drug Compounding." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on June 13, 2013. We are also responding to questions posed at the hearing by you and other Members.

If you have further questions, please let us know.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **In your testimony, you reference nine separate incidents where compounded products caused deaths and serious injuries. Please explain the actions that the FDA took following each incident. What happened to the pharmacies where these contaminated products originated?**

   Below are descriptions of the actions that FDA took in response to the nine incidents described in Dr. Woodcock's testimony. We note that most, but not all, of these adverse events were associated with product contamination:

   • *"In 1997, two patients were hospitalized with serious infections after administration of contaminated riboflavin injection prepared by a Colorado pharmacy."*

   In 1997, Riboflavin Injection made by College Pharmacy in Colorado Springs, Colorado, was administered intravenously to two patients who subsequently developed septicemia. FDA laboratory analysis of an intact vial of this drug product confirmed the presence of *Pseudomonas aeruginosa* gram-negative bacteria and a bacterial endotoxin level greater than 1,250 Endotoxin Units per milligram of riboflavin.

   In April 1999, FDA issued a Warning Letter to College Pharmacy that addressed these findings and included adulteration [§§ 501(a)(1) and 501(b)] and misbranding [§§ 502(a) and 502(j)] violations of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

   FDA's Office of Criminal Investigations (OCI) later initiated a criminal investigation into the owner and operator of College Pharmacy, Thomas Bader, and referred its case to the Justice Department. In January 2010, Bader was convicted on 31 counts related to the distribution of human growth hormone (HGH) that was smuggled into the United States from China, and the distribution of an anabolic steroid to customers with no legitimate relationship to physicians. He was found guilty on two counts of conspiracy, including conspiracy to facilitate the sale of misbranded and unapproved Chinese-made HGH, and conspiracy to manufacture, distribute, dispense, and possess with intent to distribute anabolic steroids; 27 counts of distribution of HGH; one count of facilitating the sale of smuggled HGH; and one count of possessing with intent to distribute HGH. In June 2010, Bader was sentenced to serve 40 months in Federal prison and was ordered to forfeit $4.8 million and the pharmacy building. College Pharmacy remains in operation, but under different ownership.

• *"In 2001, 13 patients in California were hospitalized and 22 received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result."*

In May 2001, FDA was notified that Doc's Pharmacy of Walnut Creek, California, shipped vials of betamethasone injection that were contaminated with *Serratia marcescens* to six health care facilities in California. Thirty-eight patients received the contaminated steroid; 13 patients were hospitalized, 22 received follow-up medical care, and three patients died. FDA needed to obtain an Administrative Warrant to complete an inspection of Doc's Pharmacy and documented several deficiencies in the firm's processes for the production of sterile drugs. In July 2001, an administrative law judge ordered the pharmacy to halt all compounding operations. The owner violated the Order, and the California Board of Pharmacy suspended his Pharmacist License in November 2001. The owner surrendered his license in March 2002, and Doc's Pharmacy was sold.

• *"In 2002, five patients in North Carolina suffered from fungal meningitis resulting from contaminated methylprednisolone acetate made by a South Carolina pharmacy. One person died."*

This incident refers to five cases of fungal infections, including one death, resulting from methylprednisolone acetate contaminated by Urgent Care Pharmacy in Spartanburg, South Carolina. FDA and the South Carolina Board of Pharmacy (SC BOP) conducted a joint inspection, and the SC BOP imposed a Cease and Desist Order. FDA recommended an immediate recall of all injectable drug products made by this facility, and although the firm initially refused to comply with this recommendation, it ultimately agreed to voluntarily recall all methylprednisolone acetate sterile injectables. FDA issued an alert warning the public about Urgent Care's injectable drugs, and the pharmacy subsequently closed permanently.

• *"In 2005, contaminated cardioplegia solution, made by a firm located in Maryland, resulted in five cases of severe systemic inflammatory infections; three of these patients died."*

Five patients were hospitalized with severe systemic inflammatory infections and three of these patients died after receiving cardioplegia solution during open heart surgery that was made by Central Admixture Pharmacy Services (CAPS) in Lanham, Maryland. After FDA laboratories identified gram-negative rods in two lots of the firm's cardioplegia solution, CAPS recalled all injectable drug products made at this facility, and FDA posted a Medical Products Safety Alert on its website notifying health care professionals about the product recall. FDA also inspected the CAPS' facility in Lanham, Maryland, and several other CAPS facilities, and then met with CAPS' management to discuss the Agency's concerns regarding CAPS' compounding activities. In 2006, FDA issued a Warning Letter to CAPS' parent company, B. Braun, which addressed this incident and other deficiencies in the firm's processes for the

production of sterile drugs that FDA identified during inspections of several CAPS' sites. CAPS subsequently hired a consultant to improve its processes.

- *"In 2007, three people died from multiple organ failure after a Texas compounder sold superpotent colchicine that was as much as 640 percent the labeled strength."*

In 2007, ApothéCure, Inc. in Dallas, Texas, prepared and dispensed 72 vials of injectable colchicine, some of which were 640 percent superpotent, resulting in the deaths of three patients. FDA obtained an Administrative Warrant to complete an inspection of the firm and identified several deficiencies in the firm's processes for the production of sterile drugs. FDA's OCI investigated the incident and referred the case to the Department of Justice for criminal prosecution. In April 2012, ApothéCure and its owner pleaded guilty to two misdemeanor counts of introducing a misbranded drug into interstate commerce. In addition, the Texas Attorney General's Office brought a civil case against ApothéCure, asking for a permanent injunction and civil penalties related to the firm's compounding activities, which include misbranded, adulterated, and unapproved drug products; misbranded foods; and false advertising of drugs and dietary supplements under Texas law. Before trial in November 2012, ApothéCure's owner signed a Consent Decree with the state of Texas, enjoining his firm from distributing adulterated or misbranded drugs.

In April 2013, FDA inspected and issued an FDA Form 483[1] list of inspectional observations to ApothéCure and its related company, NuVision, reflecting deficiencies in the firms' processes for the production of sterile drugs. On April 15, 2013, ApothéCure recalled all lots of sterile products compounded, repackaged, and distributed due to sterility assurance concerns, and on April 17, 2013, ApothéCure indicated in its response to the FDA-483 that it decided not to continue doing business, effective May 31, 2013. NuVision recalled all compounded lyophilized products due to sterility assurance concerns on April 15, 2013, and FDA issued a press release on May 18, 2013, alerting health care providers about lack of sterility assurance of all sterile drug products from this facility.

- *"In 2010, FDA investigated a cluster of* Streptococcus endophthalmitis *bacterial eye infections in patients who received injections of Avastin repackaged by a pharmacy in Tennessee."*

FDA attempted an inspection of Health and Wellness Compounding Pharmacy in Nashville, Tennessee, after learning of a cluster of *Streptococcus endophthalmitis* bacterial eye infections in patients who received injections of Avastin repackaged by this pharmacy. FDA needed to obtain an Administrative Warrant after the pharmacy's owner refused to allow FDA to inspect. Based on findings from the inspection, FDA determined that the firm was, at that time, operating as a pharmacy, and therefore, referred the incident to the Tennessee Board of Pharmacy.

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[1] An FDA Form 483 is issued when investigators observe any significant objectionable conditions. It does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of our relevant regulations, but the observations often serve as evidence of a violation of the FD&C Act and its implementing regulations.

• *"In 2011, there were 19 cases of* Serratia marcescens *bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products."*

In 2011, Advanced Specialty Pharmacy dba Meds IV (Meds IV), located in Bessemer, Alabama, prepared and dispensed total parenteral nutrition (TPN) drug products contaminated with *Serratia marcescens*, which resulted in 19 infections, including nine deaths. After learning of this incident, FDA, the state, and the Centers for Disease Control and Prevention (CDC) inspected, and the firm recalled, all intravenous drug products that it produced in 2011. FDA issued a Warning Letter to Meds IV, including adulteration [§ 501(a)(2)(A)] and misbranding [§§ 502(a) and 502(j)] violations of the FD&C Act. Meds IV subsequently surrendered its pharmacy license to the Alabama Board of Pharmacy.

• *"In 2012, 43 patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss."*

FDA and the Florida Department of Health conducted a joint inspection of Franck's Lab in Ocala, Florida, after receiving reports of fungal endophthalmitis in patients who were administered ophthalmic injections of Brilliant Blue G and triamcinolone made by this firm. Franck's Lab subsequently ceased sterile compounding operations and after FDA's environmental sampling of the firm's clean room revealed the presence of microorganisms and fungal growth, the firm announced a recall of all sterile human and veterinary prescriptions distributed from November 21, 2011, to May 21, 2012. FDA issued MedWatch statements warning health care providers of the infections and alerting them to the recalls. FDA issued a Warning Letter to the firm, including adulteration [§§ 501(a)(2)(A) and 501(c)] and misbranding [§ 502(a)] violations of the FD&C Act. The owner of Franck's Lab sold the facility to Wells Pharmacy Network, but he still owns an infusion pharmacy, Trinity Healthcare, in Ocala, Florida.

• *"Recently, in 2013, FDA investigated reports of five cases of eye infections in patients who received Avastin repackaged by a pharmacy in Georgia. The Avastin was contaminated with bacteria."*

After learning of eye infections in patients who received Avastin repackaged by Clinical Specialties Compounding Pharmacy in Augusta, Georgia, FDA inspected and issued to the firm an FDA-483 list of inspectional observations reflecting deficiencies in the firm's processes for the production of sterile drugs. Clinical Specialties voluntarily recalled all lots of sterile drug products repackaged and distributed by the firm between October 19, 2012, and March 19, 2013, due to lack of sterility assurance. In its response to the FDA-483, Clinical Specialties indicated that it was permanently discontinuing the production of sterile drug products at its facility, effective March 8, 2013, and that it did not intend to prepare or sell sterile products in the future.

2. **More likely the FDA has gone through extensive self-evaluation to fully comprehend every single regulation related to compounding. You are likely more**

knowledgeable now about the current compounding regulations than you were six months ago. It would be invaluable for this subcommittee to know exactly what the FDA can do before we determine what you cannot do. So, please explain the tools you currently have.

Under the law as it existed as of the date of the hearing, section 503A of the FD&C Act provided FDA some authority to regulate what drugs can be compounded. For example, under section 503A, FDA could, through rulemaking, establish a list of drugs that may not be compounded because the drugs or their ingredients have been withdrawn or removed from the market because the drugs or their ingredients "have been found to be unsafe or not effective." FDA could also establish a list of drugs that present "demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness" of the drug and, therefore, may not be compounded. However, due to legal challenges regarding constitutionality of the law, under the law as it existed as of the date of the hearing, section 503A did not apply nationwide. Furthermore, FDA's authority to regulate compounded drugs is more limited than our authority over conventional manufacturers. For example, under section 510 of the FD&C Act, if certain criteria are met, compounding pharmacies are not required to register with FDA or report adverse events. As a result, FDA has limited knowledge of pharmacy compounders and limited ability to oversee their activities.

In 2002, the U.S. Supreme Court had held the advertising, solicitation, and promotion provisions in section 503A unconstitutional, and, at the time of the hearing, there were conflicting court decisions on whether the unconstitutional provisions could be severed from the remainder of the statute.

On November 27, 2013, the President signed Public Law 113-54, the Drug Quality and Security Act (DQSA), which removes certain provisions from section 503A of the FD&C Act that were found to be unconstitutional by the U.S. Supreme Court in 2002. The new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide. The DQSA also creates a new section 503B in the FD&C Act. Under section 503B, a compounder can become an "outsourcing facility." Outsourcing facilities will register under section 503B; however, the legislation did not change the exemptions from registration for pharmacies under section 510 of the FD&C Act.

3. **Between 2002 and 2012, NECC was the subject of a least 52 adverse event reports. Numerous offenses were documented throughout investigations at NECC undertaken by both the FDA and state regulators. Why did the Agency not shut down NECC after these inspections? Did NECC challenge the FDA's authority to inspect?**

FDA is unable to comment specifically on NECC due to the ongoing investigations.

The Honorable Marsha Blackburn

1. **I am concerned about the growing incidence of skin cancer in the United States and the significant delay in proving the latest sunscreen technology to help address this risk from exposure to the sun's harmful rays. According to the Skin Cancer Foundation, Americans are diagnosed with more than 3.5 million cases of skin cancer each year and 1 American dies every hour from Melanoma, the most deadly form of skin cancer.**

   I understand that the FDA created the Time and Extent Application (TEA) process in 2002 to streamline applications for over-the-counter applications, such as sunscreens, however FDA has not made a final decision on any product through the TEA process. In fact, eight new sunscreen ingredients have been waiting for FDA review, some for over 10 years. The TEA process is clearly broken and needs to be reformed.

   a) **In light of the public health epidemic regarding skin cancer, please explain significant delay in making a final decision on any of the 8 pending sunscreen applications.**

   b) **Please also explain why taking final action on the 8 pending sunscreen applications has been on the FDA's Unified Agenda as a priority since 2008, however no action has been taken.**

   In the 1970s, sunscreens were used primarily on a seasonal basis to prevent sunburn among consumers with the fairest skin coloration, and sunscreen active ingredients were not thought to penetrate beyond the skin surface. Today, sunscreens are used routinely by a large percentage of the population and in large amounts covering a much greater body surface area, with the result that the extent and duration of consumers' exposure to sunscreen ingredients is orders of magnitude greater than it was in the 1970s. There is also increasing evidence that some sunscreen ingredients can be absorbed through the skin, leading to systemic exposures to these agents that were not previously anticipated or evaluated. These shifts in sunscreen usage, together with advances in scientific understanding and safety evaluation methods, have given rise to new questions about what information is needed and available to support general recognition of safety and effectiveness for both currently marketed sunscreens and ingredients seeking inclusion in the monograph via the Time and Extent Applications (TEA) process.

   Within FDA, there has been an active examination of these important scientific questions, one result of which was significant new rulemaking in 2011 that focused primarily on updated efficacy testing and related labeling issues. We also are engaged in an ongoing internal evaluation of current sunscreen safety issues and evidentiary standards, which is directly informing our evaluation of all sunscreen active ingredients, including the eight TEA ingredients.

The TEAs ask FDA to include eight new sunscreen active ingredients in the Over-the-Counter (OTC) Drug Review, also known as the OTC drug monograph system. In brief, TEA reviews are regulatory proceedings that are inherently complex and must compete for resources and priority with other OTC monograph reviews and proceedings, among other FDA activities. As noted above, FDA is currently evaluating important scientific questions relating to OTC sunscreen ingredients. Because of the public health importance of OTC sunscreens, FDA is actively working to complete our review of these TEA ingredients and expects to take action on them in the near future. We are committed to finding ways to facilitate the marketing of additional OTC sunscreen products, but we must ensure their safety, effectiveness, and overall risk-benefit profile.

To elaborate, the pace of FDA's ongoing review of the sunscreen TEAs is best understood in the context of the overall OTC drug monograph system, of which the TEA process is a part. In brief, the FD&C Act requires FDA review and approval of a new drug application (NDA) for all new drugs before they may be marketed in the United States. To avoid "new drug" status, as defined in the FD&C Act, a drug must be generally recognized as safe and effective (the GRAS/E standard), and must also have been marketed to a material extent and for a material time under the conditions described in its labeling (the material time-and-extent standard). The OTC Drug Review is a multi-step notice-and-comment rulemaking procedure that was established in 1972 to review the safety and effectiveness of OTC drugs then or previously marketed in the United States (which were presumed to satisfy the material time-and-extent standard) and provide a regulatory mechanism (the OTC monograph system) allowing OTC drug products that were found to be GRAS/E to be marketed under an applicable OTC monograph rather than product-specific NDAs. OTC drug monographs are FDA regulations that describe conditions, including specified active ingredients, for marketing various categories of OTC drugs (such as sunscreens).

The TEA process (21 CFR § 330.14) was established in 2002 to provide a pathway to OTC monograph status for additional active ingredients and other conditions not marketed in the United States for OTC use prior to the establishment of the OTC Drug Review, by enabling sponsors to establish that a condition satisfies the material time-and-extent requirement based on historic marketing data other than the date of U.S. market entry. This is done by submitting a TEA containing the required marketing data, which is reviewed by FDA to determine whether or not the condition is eligible to be considered for inclusion in an OTC monograph (eligibility determination).

TEA ingredients and other conditions must satisfy the same GRAS/E standard and evidentiary requirements that apply to other active ingredients and conditions under the general OTC monograph process. And, consistent with the general monograph process, ingredients found eligible for review under TEA applications are subject to multi-step notice-and-comment rulemaking procedures before they may be included in a final OTC drug monograph. FDA has issued eligibility determinations for all TEAs submitted to date, and all eight sunscreen TEAs were found eligible to continue to the next stage of the TEA process, the GRAS/E determination, which is now ongoing.

c) **Will you commit to work with Congress and stakeholders to enact reforms to the TEA process that will ensure that sunscreen products receive a transparent review and a predictable timeline for consideration?**

FDA is willing to work with Congress and stakeholders on this issue.

2. **As you may know, on January 1, 2013, CMS made a technical change to its billing methodology for compounding pharmacies providing drugs used in implanted pain pumps. This change requires pharmacies to sell these compounded medications to physicians who then re-sell then to the patient and bill Medicare. Prior to January 1st, pharmacies were not required to sell drugs to the physician and instead could bill Medicare directly. To further complicate the matter, the Tennessee Board of Pharmacy does not allow pharmacies to sell these compounded medications to physicians for resale to patients. This practice is also illegal in Mississippi, and other state Boards of Pharmacy are assessing the impact of CMS' change on pharmacy practice. I am concerned that this technical change has jeopardized access to necessary pain medications for some of Medicare's most vulnerable beneficiaries. Even more, this change – prohibiting pharmacies from billing Medicare directly – eliminates an important accreditation requirement designed to protect patient safety. Pharmacies billing Medicare directly for these drugs must comply with Medicare supplier standards and federal regulations, such as U.S. Pharmacopeia 797. These standards provide an additional layer of quality promotion and patient safety for pharmacies compounding and dispensing sterile products for use in implanted pain pumps.**

Saying all of this, do you find it concerning the CMS – in the wake of the tragic out break, in spite of state pharmacy law, and in spite of stakeholder opposition – is encouraging pharmacies to sell drugs directly to physicians as opposed to billing Medicare directly and complying with quality accreditation standards?

For at least 20 years to 2013, pharmacies had billed Medicare directly for these patient specific compounded medications, and the National Home Infused Association supports legislation sponsored by Congressman Harper (HR 232) which would restore access to these therapies for beneficiaries. Saying all of this, do you find it concerning that CMS – in the wake of a tragic outbreak, in spite of state pharmacy law, and in spite of stakeholder opposition – is encouraging pharmacies to sell drugs directly to physicians as opposed to billing Medicare directly and complying with quality accreditation standards?

As these questions relate to CMS' reimbursement policies, we recommend contacting CMS with these questions.

3. **As you may or may not know, the State of Tennessee recently passed legislation that allows pharmacies to compound products for use in a practitioner's office for**

administration to that prescribing practitioner's patients – a practice known as "office use" compounding. It is my understanding that 43 other states also allow for office use compounding.

a) **What is the Agency's position regarding traditional compounding taking place in an office setting?**

b) **Should this be regulated by the FDA or State Board of Pharmacies? Please explain.**

In light of recent outbreaks associated with sterile drugs produced by pharmacies, the Agency has taken a critical look at our surveillance and enforcement approach to pharmacies that produce compounded drugs. Over the past year, FDA has conducted numerous for-cause and proactive inspections of firms that produce compounded drugs. The Agency continues to evaluate the information obtained during the inspections.

Since the hearing, the President signed the DQSA. Under the DQSA, hospitals and health care professionals can purchase compounded drugs without a prescription from a compounder that is registered as an outsourcing facility under section 503B. Section 503A requires, among other things, that, to qualify for the exemptions under section 503A, there be a prescription for an identified individual patient. The Agency intends to exercise its authority, as appropriate to protect the public health, against compounded drugs that do not qualify for the exemptions in section 503A or section 503B, and drugs that are adulterated or misbranded or otherwise violate Federal laws.

The Honorable Renee Ellmers

1. **Are compounders making the same products that drug-manufacturers make? I know it may be in a different form, but is it the same product?**

Compounders sometimes take FDA-approved products and dilute them to achieve a different strength, or they may make a liquid or suppository. They may also make drugs from bulk active ingredients. This may be done, for example, to make a product without an allergen, such as peanut oil, that some patients cannot tolerate. Many compounders do make products that appear to be only slightly different from those made by traditional drug manufacturers. For example, they might make an 8 mL vial of a product when the FDA-approved product is available in 10 mL vials. Although these products may appear to be similar to FDA-approved drug products, it is important to remember that compounded drugs do not undergo the same premarket review as FDA-approved drugs and thus lack an FDA finding of safety and efficacy, as well as manufacturing quality. The active ingredients may come from sources that have not been reviewed by FDA, and the methods by which they are made have not been reviewed to determine whether they are adequate to produce a safe, pure, and potent product.

2. Currently, do compounders have the same regulations and requirements that drug manufacturers have? Why or why not?

Under current Federal law, when certain conditions are met, compounding pharmacies are not subject to the same requirements as drug manufacturers. For example, compounding pharmacies, but not drug manufacturers, are exempt from certain requirements under the FD&C Act, as described below.

These disparate requirements derive from the FD&C Act. Section 503A, added to the FD&C Act in 1997 as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FD&C Act requiring:

- Compliance with CGMP requirements (section 501(a)(2)(B));
- Labeling with adequate directions for use (section 502(f)(1)); and
- FDA approval prior to marketing (section 505).

Drugs produced by compounders must meet the conditions of section 503A to qualify for the exemptions specified in that section. All other applicable provisions of the FD&C Act remain in effect for compounded drugs, even if the conditions in section 503A are met. For example, a compounded drug cannot be contaminated or made under insanitary conditions (see sections 501(a)(1) and 501(a)(2)(A)). And if a compounded drug does not qualify for the exemptions under section 503A of the FD&C Act, the compounded drug would be subject to all of the requirements of the Act that are applicable to drugs made by conventional manufacturers, including the new drug approval, CGMP, and adequate directions for use.

However, at the time of the hearing, the validity of section 503A of the FD&C Act was uncertain. Section 503A FD&C Act had been challenged in court, and there were conflicting court rulings regarding the validity of this section. Since the hearing, President Obama signed the DQSA, which removes certain provisions from the FD&C Act that the U.S. Supreme Court held unconstitutional. By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide.

3. What are the changes to compounding you propose making in order to prevent the meningitis outbreak last year and ensure compounded products are safe?

On April 16, 2013, FDA Commissioner Margaret Hamburg outlined the Agency's proposed framework for improving oversight of compounding in testimony before this Committee. Please see attached document (*April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*).

4. Is there a limit to how much product a compounder can make?

Under current Federal law, there is no limit to how much product a compounding pharmacy can make. Section 503A of the FD&C Act places a limit on the volume of drugs that may be shipped interstate. Under that provision, a pharmacy may only distribute interstate compounded drugs in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician, unless the state in which the pharmacy is located has entered into a memorandum of understanding (MOU) with the Agency that addresses the distribution of inordinate amounts of compounded drugs interstate and provides for an appropriate investigation by the state of complaints related to compounded products. FDA published a draft MOU in 1999, and received over 6,000 comments. However, due to the conflicting court rulings that had resulted in uncertainty regarding the validity of section 503A, the template MOU was never finalized, and FDA has not been implementing the provision.

However, on November 27, 2013, the President signed DQSA, which removes the provisions from section 503A of the FD&C Act that were found to be unconstitutional by the U.S. Supreme Court in 2002. By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide. FDA has initiated actions to implement the new law.

5. **You testified before the Senate HELP committee regarding their legislation on May 9, 2013. Under this legislation, would compounded drugs manufactured by the new entity (compounding manufacturer) be subject to the same requirements as current manufacturers under the Federal, Food, Drug, and Cosmetic Act?**

    a. **If yes, can you describe those requirements?**
    b. **If no, how are those standards – different – and why are they different?**

As of the time of the hearing, the legislation proposed by the Senate HELP committee, S. 959, would have placed several requirements on "compounding manufacturers" that are similar to those imposed on traditional manufacturers. For example, as drafted, S. 959 would have:

- Required compounding manufacturers to meet FDA-established product quality standards, to register with FDA, and to list the products they produce.

- Required compounding manufacturers to report serious adverse events, of which they become aware, to FDA and to label their products with important information for physicians and consumers.

- Provided FDA with the clear authority to access records of compounding manufacturers during an inspection to more effectively oversee their compounding activities.

- Put in place several restrictions—applicable to both traditional compounders and compounding manufacturers—on the types of bulk drug substances that can be used to compound a drug and would prohibit the compounding of copies of marketed FDA-approved drugs, unless they appear on FDA's drug shortage list.

- Provided that compounding of other categories of drug products, such as complex dosage forms and biologics, would be prohibited because they are particularly difficult to make.

- Required compounding manufacturers to pay establishment fees and, when appropriate, re-inspection fees, to help defray the costs of this increased oversight.

Not all requirements imposed on manufacturers under the FD&C Act, however, would have applied to compounding manufacturers under S. 959. For example, compounding manufacturers would not be required to submit an NDA for compounded products.

6. How do drug manufactures today assure the raw materials (or Active Pharmaceutical Ingredient "API") used to create a drug are safe? What is the certification process?

For finished dosage forms (FDFs) required to have an application approved before marketing, FDA reviews API production processes before granting marketing approval of an FDF using the API. In addition, the FD&C Act requires producers of APIs (and excipients, or inactive ingredients) and producers of the FDF to follow CGMP requirements appropriate to the manufacture of the drug (API, excipients, or FDF). FDA regulates the manufacture of APIs under internationally harmonized CGMP guidance for industry, known as ICH Q7. The CGMP requirements, if followed, ensure that APIs have the safety, identity, quality, and purity as labeled. FDA inspects API production facilities referenced in approved applications to verify conformance with ICH Q7 and CGMPs.

FDA requires conventional manufacturers of the FDFs (e.g., tablets, capsules, injections) to exercise additional controls over the quality of APIs before use in FDF manufacturing. Specifically, the CGMP regulations for finished pharmaceuticals (primarily at 21 CFR parts 210-211) require FDF manufacturers to examine the integrity of each API shipment and to test samples verifying each ingredient's identity before it can be released for FDF production. FDA regulations, however, do not require FDF manufacturers of non-application drug products (e.g., OTC drugs covered by a published monograph at 21 CFR 330-358) to know who actually manufactures the API, and some APIs are purchased from wholesalers and brokers. For those products requiring an approved new drug application, FDA also reviews FDF production processes before marketing approval, and inspects FDF production facilities on a risk-based schedule to verify conformance with 21 CFR 211 and CGMPs.

Drug compounders, which are not subject to FDA application approval and CGMP requirements, may not routinely evaluate the quality of the APIs they use in compounding. Compounders that do not check each shipment or that do not verify their API supply chain are at significant risk of producing a finished product that does not contain the API they intended, does not function as intended, or contains harmful impurities.

7. **How do compounders access the API they use? Is their API FDA-approved?**

The Agency does not generally approve bulk APIs used in the manufacture or compounding of drug products, nor are the APIs used in compounding required to be FDA-approved.

8. **Don't drug manufacturers pay much more than a compounding manufacturer would under the User Fee structures? Why aren't compounders paying more if they are making the same product? Or more importantly, if I'm an FDA – licensed drug maker, why don't I just become a compounder? It would be cheaper and a lot less paper work?**

As you note, the user fees paid by drug manufacturers are significantly higher than those a compounding manufacturer would pay under the legislation under consideration as of the time of the hearing or that an outsourcing facility will pay under the DQSA. Pharmacies compounding drugs under the conditions in section 503A will continue to pay no user fees at all. However, there are a number of reasons that drug manufacturers would not opt to become a compounder. For example, only state-licensed pharmacists or physicians may qualify for the exemptions in section 503A of the FD&C Act, and the pharmacists or physicians must compound the drugs consistent with the conditions of section 503A. Under section 503A, a pharmacy may not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product. Further, under section 503A a pharmacy may only distribute interstate compounded drugs in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician, unless the state in which the pharmacy is located has entered into an MOU with the Agency that addresses the distribution of inordinate amounts of compounded drugs interstate and provides for an appropriate investigation by the state of complaints related to compounded products.

9. **There is some talk that compounding manufacturers could be utilized to help end drug shortages. Currently, how are drug shortages determined? Are there different levels of drug shortages?**

The CDER Drug Shortage Staff (DSS) utilizes information from manufacturers, other FDA offices, external entities, and market-share data to determine or verify that a shortage exists.

Consistent with FDASIA, DSS defines a drug shortage, with respect to a drug, to mean a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.

The severity of the drug shortage situation for a given product may vary depending on certain circumstances, such as the length of the potential shortage/supply interruption and the number of other available manufacturers for that product, and whether they are also experiencing a shortage situation or whether they are able to increase production to meet the anticipated market shortfall.

10. Is the FDA drug shortage list the only list used?

The American Society of Health-System Pharmacists[2] (ASHP) lists drug shortages and additional information on its website. Although both ASHP and FDA maintain drug shortage lists, the information received and displayed regarding drug shortages varies between the two lists. For example, FDA's drug shortage list focuses mainly on drugs that are considered medically necessary,[3] while ASHP's list includes more drugs; some that are not medically necessary because there are suitable alternatives available.

11. How does a drug get off the drug shortage list? Who determines that?

For the drug products listed on the drug shortage list, DSS is in regular communication with relevant manufacturers regarding their current and projected drug supply and utilizes this information to help determine the supply status and potential path forward, if applicable. DSS may also consider information from other FDA offices, external entities, and market-share data. Once a drug product is available from the involved manufacturers and supply is sufficient to meet the demand or projected demand, DSS removes the drug product listing from the current drug shortage list and places it in the resolved drug shortage list, which is also on the FDA drug shortage website.[4]

12. For products on the drug shortage list, many of which are sterile injectable drugs, should a compounder be held to the same level of standards and requirements as the current manufacturers?

Patients expect and deserve high-quality drugs. Patients should have access to compounded medicines that are safe, pure, and potent.

FDA's testimony referenced a series of adverse events associated with compounded drugs, primarily sterile injectables, over the last 10 years, and FDA is concerned about

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[2] *http://www.ashp.org/*

[3] A medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug in adequate supply that is judged by medical staff to be an adequate substitute. Off-label uses are taken into account when making medical-necessity determinations. FDA's drug shortage list includes all shortages that the Agency has been informed of and verified, which are mostly shortages of medically necessary drugs.

[4] *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm314739.htm*

compounders that produce such high-risk sterile drugs without the necessary controls to ensure quality.

Under FDA's proposed framework (please see attached document, *April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*), as presented at the time of the hearing, pharmacies that produce sterile drugs in advance of or without a prescription and ship those drugs interstate would be subject to Federal oversight and uniform quality standards. These types of sterile compounding operations pose higher risks and, therefore, should be subject to uniform quality standards, established by FDA and appropriate to the activity, including when they are making drugs on the drug shortage list.

Since the hearing, President Obama signed the DQSA, which created a new section 503B in the FD&C Act. Under section 503B, a compounder can become an outsourcing facility and can compound drugs in shortage, so long as certain criteria are met, including compliance with CGMPs.

13. How many drug shortages would be relieved if compounders mass-manufactured product?

The Agency cannot estimate the number of drug shortages that may be relieved if compounders produced drug products in shortage. However, we note that under the recently enacted DQSA, which added section 503B to the FD&C Act, outsourcing facilities may now begin to play a role in compounding drug products that are in shortage. (Please see Question #6, from Ms. Ellmers, for additional information on requirements for APIs in FDA-approved products.)

With respect to drug shortages generally, it is often difficult to forecast the drug product(s) that may become in short supply or the duration of such shortages, since immediate and projected supply from drug manufacturers can change rapidly and unexpectedly due to many factors. FDA works hard, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations.

14. How would the safety of these compounded drugs be assured? What are the testing processes?

Under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would have been subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.

To further ensure the safety of compounded drugs, FDA proposed that it have clear ability to collect and test samples of compounded drugs and to examine and collect records in a compounding pharmacy, just as the Agency does when inspecting other

manufacturers. FDA also proposed that it have clear authority to examine records, such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, to respond to public health threats, and to enforce Federal standards.

15. **Will there be any differences between the standards and regulations of the compounding manufacturer and today's manufacturers?**

As of the time of the hearing, the legislation proposed by the Senate HELP committee, S. 959, would have created a new category of drug producers called "compounding manufacturers." The recently enacted DQSA created a new category of drug producers called "outsourcing facilities." Among other significant differences, unlike conventional manufacturers, outsourcing facilities are not required to obtain an approved new drug application (NDA) for their compounded drugs, provided they meet certain conditions.

16. **Can you provide more clarity/detail on the differences between the two levels of standards between today's manufacturers and the compounding manufacturer?**

FDA cannot provide more clarity or detail on what the differences in the standards applicable to conventional manufacturers and compounding manufacturers would have been under the legislation being considered at the time of the hearing, because that legislation was never enacted or implemented.

Under the recently enacted DQSA, outsourcing facilities are subject to section 501(a)(2)(B) of the FD&C Act, which requires compliance with CGMPs. FDA is looking at its CGMP regulations to determine what requirements are appropriate for outsourcing facilities.

17. **If the full requirements and standards are different for products on the drug shortage list produced by a compounding manufacturer than those of today's manufacturers, how will this ensure the greatest level of confidence and safety in the products?**

As stated above, under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would be subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.

18. **Do doctors and hospitals tell a patient that the drugs they are receiving are manufactured by a compounding manufacturer?**

Health care providers and patients often are unaware that they administered or received a compounded product, which limits their ability to associate any adverse events with a compounded product. This hinders FDA's ability to effectively identify adverse events for compounded products in our adverse event reporting system. At the time of the hearing, FDA was working with Congress on its proposed framework, which included potential improvements such as label statements for compounded products to help patients and providers make more informed choices.

19. **Should hospitals and providers require a patient to sign a release for any liability if the hospital or provider gives a compounded drug that is not manufactured under the same safety requirement of the drug manufacturers?**

FDA does not have a position on this.

Additional Information for the record

During the hearing, Members asked FDA to provide additional information for the record. Descriptions of the requested information, based on the relevant excerpts from the hearing transcript regarding these requests, are provided below. We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **You testified during the hearing that several companies have challenged your authority while the FDA was conducting inspections. Please provide a list to the committee of companies that the FDA inspected those that challenged your authority, and the grounds by which the companies challenged your authority.**

The response below was e-mailed to Representative Pitts' Health Policy Analyst on July 16, 2013, in response to this question.

In a sample of 226 pharmacy inspections[5] between 2002 and 2012 that FDA has conducted on practices related to pharmacy compounding of human and veterinary drugs, pharmacies have refused at least one FDA request in more than 25 percent of inspections. For example, 4 percent of firms refused FDA entry into their facility, and of those firms that did grant entry, 12 percent refused FDA access to records (e.g., shipping records, dispensing records, product formulas, and/or standard operating

[5] These 226 inspections represent the number of inspections recorded under the human and veterinary pharmacy compounding Program Assignment Codes (PAC Code) between 2002 and September 25, 2012, that FDA has conducted of pharmacies based on practices related to pharmacy compounding of human and veterinary drugs. Not all compounding pharmacy inspections were recorded under this PAC Code, in part, because some firms engage in multiple types of activities. In addition, some inspectional activities may have been coded as "investigations" rather than "inspections" and, therefore, not captured in this figure. Thus, we know that FDA conducted additional inspections of firms that could be classified as compounding pharmacies that are not accurately reflected in our databases.

procedures). Other refusals include the ability to observe drug production processes, collect samples, access portions of the facility, or take photographs.

FDA encountered refusals of at least one FDA request during inspections of the following compounding pharmacies between 2002 and September 25, 2012. This may not be an exhaustive list:

2002

- Lee and Company, Inc. dba Lee Pharmacy, Fort Smith, AR (July 2002)
- Med-Mart Pacific Pulmonary Services Pharmacy, Bakersfield, CA (November 2002)

2003

- Plum Creek Pharmaceuticals, Inc., Amarillo, TX (February 2003)
- Med 4 Home Pharmacy, Kansas City, MO (March 2003)
- Med-Mart Pacific Pulmonary Services Pharmacy, Bakersfield, CA (May 2003)
- Unique Pharmaceutical, Ltd., Temple, TX (August 2003)
- Monument Pharmaceutical Co., Inc., Winchester, VA (September 2003)

2004

- Keyes Drug, Newton, MA (April 2004)
- Reliant Pharmacy, Southaven, MS (May 2004)
- Reliant Pharmacy, Southaven, MS (June 2004)
- Essential Pharmacy Compounding, Omaha, NE (August 2004)
- Pet Script, Inc., Paris, TX (August 2004)
- University Rx Specialties, Inc. (September 2004)
- ApothéCure, Inc., Dallas, TX (September 2004)
- Kubat Custom Healthcare, Omaha, NE (September 2004)

2005

- PharMEDium Services, Sugar Land, TX (March 2005)
- Pulmo-Dose Inc., Murray, KY (August 2005)
- Civic Center Pharmacy, Scottsdale, AZ (October 2005)
- Pharmacy Creations, Randolph, NJ (October 2005)
- Wedgewood Village Pharmacy, Swedesboro, NJ (October 2005)
- Alchemist Shoppe, P.C., Denville, NJ (November 2005)
- Spoonamore Drug Co., Inc., Louisville, KY (December 2005)

2006

- Pharmacy Creations, Randolph, NJ (February 2006)
- D.R. Pharmacy, Inc., Midland, TX (March 2006)
- Oakdell Pharmacy, Inc., San Antonio, TX (April 2006)
- Hopewell Pharmacy and Compounding Center, Hopewell, NJ (October 2006)

2007

- Newman Inc. dba Medi-Stat, Mobile, AL (February 2007)
- ApothéCure, Inc., Dallas, TX (May 2007)
- Advanced Physician Solutions, Inc., North Hollywood, CA (July 2007)
- Leiter's Pharmacy, San Jose, CA (September 2007)
- Calvert-Gamble Pharmacy, Inc. dba Southern Meds Joint Venture, Biloxi, MS (October 2007)
- Delta Pharma, Inc., Ripley, MS (October 2007)
- Wellness Pharmacy, Birmingham, AL (November 2007)
- Bellevue Pharmacy Solutions, Inc., Saint Louis, MO (November 2007)
- Spoonamore Drug Co., Inc., Louisville, KY (December 2007)

2008

- PharMEDium Services LLC, Cleveland, MS (January 2008)
- AnazaoHealth Corporation, Tampa, FL (May 2008)
- Hopewell Pharmacy and Compounding Center, Hopewell, NJ (June 2008)
- Specialty Pharmacy of Saint Louis, Saint Louis, MO (July 2008)
- National Respiratory Services LLC, Louisville, KY (July 2008)
- Precision Pharmacies, LLC, Bakersfield, CA (August 2008)
- Advanced Physician Solutions, Inc., North Hollywood, CA (August 2008)
- University Pharmacy, Salt Lake City, UT (November 2008)

2009

- Medaus, Inc., Birmingham, AL (February 2009)
- Lee and Company, Inc. dba Lee Pharmacy, Fort Smith, AR (February 2009)
- Prescription Lab Compounding Pharmacy, Tucson, AZ (February 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (May 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (June 2009)
- Central Admixture Pharmacy Services, Inc., Chicago, IL (August 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (December 2009)

2010

- Preckshot Professional Pharmacy, Peoria Hill, IL (June 2010)
- Health & Wellness Compounding Pharmacy, Nashville, TN (August 2010)
- Delta Pharma, Inc., Ripley, MS (September 2010)
- Alwan Pharmacy, Peoria, IL (December 2010)

2011

- Infupharma LLC, Hollywood, FL (September 2011)

2012 (January 2012 through September 25, 2012)

- Weatherford Compounding Pharmacy LLC, Weatherford, TX (February 2012)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (May 2012)

In addition, between 2002 and October 2012, FDA sought administrative warrants in 25 cases, of which nearly half were for compounding pharmacies. This covers all product areas, not just firms producing drugs. Below are some specific examples of situations in which FDA needed to obtain warrants to inspect compounding pharmacies. Although FDA was ultimately able to obtain warrants to inspect, in many of these cases, the firms' refusals hindered FDA's ability to rapidly investigate reports of serious patient injury, including infections and death. This is not an exhaustive list:

Lee Pharmacy (2002)
FDA initiated an inspection of Lee Pharmacy on July 17, 2002, to investigate a complaint from a physician reporting foreign material in a preservative-free sterile injectable drug product made by this firm. Lee Pharmacy's owner refused to provide records, including distribution information identifying consignees of this product, reportedly based on advice from his attorney. Because of these refusals, FDA's inspection ended prematurely on July 18, 2002. FDA attempted another inspection on December 2, 2002, and again was refused. FDA obtained an Administrative Warrant on December 10, 2002, to complete the inspection.

ApothéCure, Inc. (2007)
FDA initiated an inspection of ApothéCure, Inc. on April 26, 2007, to investigate reports of three deaths following administration of injectable colchicine that was later found to be 640 percent superpotent. When the scope of FDA's inspection went beyond the firm's preparation of colchicine, the owner refused to provide records or allow further access to the facility, causing the inspection to conclude prematurely on May 3, 2007. On August 3, 2007, FDA obtained an Administrative Warrant to complete its inspection. OCI investigated the incident and referred the case to the Department of Justice for criminal prosecution. On April 24, 2012, ApothéCure and its owner pleaded guilty to two misdemeanor counts of introducing a drug that was misbranded into interstate commerce.

Health and Wellness Compounding Pharmacy, LLC (2010)
FDA attempted an inspection of Health and Wellness Compounding Pharmacy on April 28, 2010, after learning of a cluster of *Streptococcus endophthalmitis* infections in patients who received injections of Avastin repackaged by this firm. The owner asserted that his firm was not under FDA's jurisdiction and refused to allow FDA to inspect. On August 2, 2010, FDA obtained an Administrative Warrant to inspect the firm.

Infupharma, LLC (2011)
FDA attempted to inspect Infupharma, Inc. beginning on July 18, 2011, after receiving reports of 12 cases of *Streptococcus endophthalmitis* infections following intravitreal injections of repackaged Avastin. After a few days, the owner asserted that his firm was not subject to FDA regulations and, although he agreed to suspend repackaging of Avastin, he would not agree to cease sterile operations. The owner refused FDA access to observe processing of sterile injectable drugs, and, therefore, FDA's inspection ended prematurely on July 22, 2011. After receiving sample analysis

results confirming microbial contamination and information suggesting that Infupharma intended to resume repackaging of Avastin, FDA obtained an Administrative Warrant on September 15, 2011, to complete the inspection and later issued a Warning Letter citing the firm for adulteration, unapproved drug, and misbranding violations.

Notably, despite recent events, and although we are often working with the state inspectors, our investigators' efforts are being delayed because they are denied full access to records at some of the facilities they are inspecting. For example, during both of our recent proactive and for-cause pharmacy compounding inspections, several pharmacies delayed or refused FDA access to records. FDA encountered refusals of at least one FDA request during recent inspections of the following firms and had to seek Administrative Warrants in three cases as noted:

- Wedgewood Pharmacy, Swedesboro, NJ (November 2012) (obtained warrant)
- JCB Labs, Wichita, KS (February 2013)
- Triangle Compounding Pharmacy, Cary, NC (February 2013)
- University Pharmacy, Salt Lake City, UT (February 2013)
- Avella, Phoenix, AZ (February 2013)
- Foundation Care, Earth City, MO (March 2013)
- Olympia Compounding Pharmacy, Orlando, FL (March 2013) (obtained warrant)
- MedQuest Pharmacy, North Salt Lake, UT (March 2013)
- Pine Pharmacy, Williamsville, NY (July 2013) (obtained warrant)

The Honorable Michael Burgess

1. **There was a discussion regarding the level of difficulty of obtaining an injunction from a judge. Please provide a list of how many times you have not prevailed in obtaining an injunction? (pg. 35)**

In general, the decision whether to pursue an injunction or a seizure is a fact-specific determination that is made by FDA on a case-by-case basis. In considering an injunction or a seizure, FDA will evaluate factors such as pending and adjudicated actions involving the same charges, the seriousness of the offense, the actual or potential impact of the offense on the public, whether other possible actions could be as effective or more effective, whether a voluntary recall by the firm was refused or would be inadequate to protect the public, whether violative practices have not been corrected through use of voluntary or other regulatory approaches, and/or whether FDA would be able to demonstrate the likelihood of the continuance of the violation in the absence of a court order. Additional information is available in FDA's Regulatory Procedures Manual, Chapter 6. Due to the many legal challenges at the time of the hearing (questions regarding the validity of section 503A of the FD&C Act), identifying and pursuing civil enforcement actions against compounding pharmacies has been difficult.

Between 2002 and September 25, 2012, FDA brought one injunction against a compounding pharmacy. In 2009, 21polo ponies died after being administered a compounded animal drug made by Franck's Lab in Florida. In 2011, the U.S. District Court denied FDA's requested injunction, stating that FDA's "statutory authority to regulate traditional state-licensed veterinary pharmacy compounding was questionable." FDA appealed that decision to the 11th Circuit Court of Appeals. In October 2012, the parties filed a joint motion to dismiss the appeal and vacate the 2011 U.S. District Court decision because it was moot after Franck's sold its assets and stopped engaging in animal drug compounding. On October 18, 2012, the 11th Circuit Court of Appeals granted this motion, dismissing the appeal and vacating the lower court's decision.

Although FDA did not bring additional civil injunction cases against compounding pharmacies, since 2002, FDA has criminally investigated at least six pharmacies regarding their compounding practices, which resulted in successful prosecutions by the Department of Justice, including:

- On April 24, 2012, ApothéCure, a compounding pharmacy, and its owner pleaded guilty to two misdemeanor counts of introducing a misbranded drug into interstate commerce. The government's charges were based on ApothéCure's February 2007 shipment of 72 vials of compounded colchicine. FDA testing of the vials revealed that some of the vials were superpotent, containing 640 percent of the level of colchicine declared on the label. Other vials were determined to be subpotent and contained less than 62 percent of the declared levels on the labels. Three patients who were administered colchicine from ApothéCure died shortly afterward, and the cause of death for all three patients was determined to be colchicine toxicity.

- In February 2012, the former Vice President of National Respiratory Services, LLC (NRS), a compounding pharmacy, pleaded guilty to charges of misbranding and adulterating drugs and to committing healthcare fraud. The government's charges were based on NRS providing compounded medications to patients, but leading both Medicare and patients' doctors to believe that NRS was providing FDA-approved, commercially manufactured products. The government also alleged that the former Vice President of NRS, aided and abetted by others, misbranded inhalation drugs because the labeling misrepresented the strength and potency of their active ingredients, or the type of drug actually provided and adulterated inhalation drugs, because their strength differed from what it was purported or represented to possess and because the drugs were contaminated and non-sterile.

- In January 2010, the owner and operator of College Pharmacy, a compounding pharmacy, was convicted on 31 counts related to the distribution of human growth hormone (HGH) that was smuggled into the United States from China, and the distribution of an anabolic steroid to customers with no legitimate relationship to physicians. He was found guilty on two counts of conspiracy, including conspiracy to facilitate the sale of misbranded and unapproved Chinese-made HGH and conspiracy to manufacture, distribute, dispense, and possess with intent to distribute

anabolic steroids; 27 counts of distribution of HGH; one count of facilitating the sale of smuggled HGH; and one count of possessing with intent to distribute HGH.

- In January 2006, the owner of City Pharmacy, a compounding pharmacy, pleaded guilty to health care fraud and misbranding drugs. The government's charges were based on findings that the pharmacy dispensed compounded inhalation solutions to Medicare patients in different strengths than the commercially available drugs prescribed, while leading Medicare and the patients' physicians to believe that the pharmacy was providing the FDA-approved, commercially manufactured products.

- In August 2004, pharmacists of Tricare Pharmacy Network, a compounding pharmacy, were convicted of misbranding of a drug after receipt in interstate commerce. This was based on evidence that the pharmacy dispensed drugs bearing fictitious patient and doctors' names or that were invoiced to disguise the drug that was shipped. In addition, the pharmacy did not receive or require prescriptions for drug products dispensed.

- In July 2002, the owner of The Medicine Shoppe was convicted on three counts of manufacturing a Schedule II Controlled Substance without a prescription, two counts of misbranding and adulterating drugs, and one count of health care fraud. The government's charges were based on evidence that the pharmacy dispensed compounded drugs instead of commercially available, FDA-approved drugs to numerous patients without their knowledge and without authorization from their physicians, as well as laboratory results indicating that samples of drug products collected at the firm were ineffective.

The Honorable John D. Dingell

1. **Please explain the authority the FDA needs to require all compounding pharmacies to register with the agency.**

2. **Please explain the authority the FDA needs to require all compounding pharmacies to report adverse events.**

3. **Please explain the authority the FDA needs to require all compounding pharmacies to follow good manufacturing practices.**

4. **Please explain the authority the FDA needs to require nontraditional compounders to be subject to appropriate good manufacturing practices the way manufactures are.**

5. **What authority does the FDA need to ensure risked-based inspection schedules are appropriate for non-traditional compounders?**

6. **Please explain the authority the FDA needs to see all records when inspecting a compounding pharmacy.**

7. **Please explain the authority the FDA needs for a fee system for the approval of pharmaceuticals and medical devices.**

8. **Please explain the need for a strong user fee program.**

Please see attached document (*April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*), provided in response to all of Representative Dingell's questions.

The Honorable H. Morgan Griffith

1. **The FDA was prepared to release guidance proposals in August of 2012. Please explain why this guidance does not adequately address pharmacy compounding.**

The needed clarity, predictability, and transparency for effective regulation of this industry should be set through clear requirements in statute, particularly given the size and public health impact of this industry and affected stakeholders, including the hospitals, patients, physicians, and states. At the time of the hearing, conflicting court decisions had created uncertainty with regard to the validity of section 503A. The DQSA removed the provisions of section 503A that had been held unconstitutional and removed uncertainty with regard to the validity of section 503A, which will now be applicable to compounders nationwide.

Under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would have been subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.