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

FEB 18 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the July 16, 2013, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Reforming the Drug Compounding Regulatory Framework." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on August 13, 2013.

If you have further questions, please let us know.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

Enclosure

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

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

The Honorable John D. Dingell

1. **What authority does the FDA need to require all compounding pharmacies to register with the Agency?**

   Please see the enclosed document (*July 16th, 2013 Statement of Janet Woodcock Before the Subcommittee on Health, Committee on Energy and Commerce*), provided to respond to the following Questions 1-6, and 8, from Mr. Dingell, on necessary authorities.

2. **What authority does the FDA need to require all compounding pharmacies to report adverse events?**

3. **What authority does the FDA need to require all compounding pharmacies to follow good manufacturing practices?**

4. **Does FDA believe nontraditional compounders should be subject to appropriate good manufacturing practices like manufacturers? Please elaborate.**

5. **Does FDA believe a risked-based inspection schedule is appropriate for non-traditional compounders? Please elaborate.**

6. **What authority does the FDA need to see all records when inspecting any compounding pharmacy?**

7. **Has FDA faced litigation regarding its ability to inspect records in pharmacies? Please elaborate.**

   The following list includes the most significant legal challenges to FDA's authority over compounding since the early 1990s and the parties involved. This list is not exhaustive.

   ***Professionals & Patients for Customized Care (P2C2) v. Shalala*, 56 F.3d 592 (5th Cir. 1995)**

   - According to the International Association of Compounding Pharmacists' (IACP) website (*http://www.iacprx.org/*), P2C2 represents 164,000 patients and practitioners.

   - P2C2 challenged FDA's Compliance Policy Guide on compounding soon after it was issued in 1992 on the basis that it violated the Administrative Procedure Act's notice-and-comment rulemaking requirements.

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

- Plaintiffs were a group of seven pharmacies: Western States Medical Center Pharmacy; Women's International Pharmacy; Health Pharmacy; College Pharmacy; Wedgewood Village Pharmacy; ApothéCure, Inc.; and Lakeside Pharmacy.

- Plaintiffs challenged the constitutionality of the solicitation and advertising provisions in section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act).

***Wedgewood Village Pharmacy v. U.S.*, 421 F.3d 263 (3d Cir. 2005)**

- On March 10, 2003, FDA sought an administrative warrant from a Federal court to inspect Wedgewood's facilities and to access certain records. Wedgewood moved to quash the warrant, arguing that the FD&C Act provides state-licensed pharmacies a total exemption from FDA inspection.

***Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008)**

- Plaintiffs were a group of 10 pharmacies: Medical Center Pharmacy; Applied Pharmacy; College Pharmacy; Med Shop Total Care Pharmacy; Pet Health Pharmacy Incorporated; Plum Creek Pharmaceuticals Incorporated; Premier Pharmacy; University Compounding Pharmacy; Veterinary Pharmacies of America; Women's International Pharmacy.

- Plaintiffs sought declaratory and injunctive relief against FDA, arguing, among other things, that the Agency: 1) cannot regulate compounded drugs as "new drugs" within the meaning of the FD&C Act, and 2) cannot inspect the records of the plaintiff pharmacies because of their claim that they are exempt from a records inspection under section 704(a)(2)(A) of the Act.

***U.S. v. Franck's Lab*, 816 F. Supp. 2d 1209 (M.D. Fla. 2011)**

- After compounded drugs from Franck's Lab caused the death of 21 polo ponies, FDA sought an injunction to prevent the pharmacy from compounding animal drugs using bulk drug substances. Franck's Lab contested FDA's jurisdiction over its animal drug compounding practices.

FDA's authority to inspect has also been challenged on several occasions. In a sample of 226 pharmacy inspections[1] 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

[1]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, which 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, are 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. FDA's Office of Criminal Investigations 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 though 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 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 two 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)

8. Why does FDA need this authority to effectively regulate compounding pharmacies?

The legal framework at the time of the hearing did not provide FDA with the tools needed to identify and appropriately regulate these pharmacies to help *prevent* product contamination and patient harm. Under section 510 of the FD&C Act, we did not have the authority to require registration of pharmacies that meet certain criteria, so we did not have a list of all of the pharmacies that produce drugs, and we did not know what drugs they are making. While the newly enacted Drug Quality and Security Act (DQSA, P.L. 113-54) provided that outsourcing facilities may register with FDA, the DQSA did not amend section 510. Because of this, our ability to conduct pro-active, risk-based inspections was and remains limited to those pharmacies of which we already had knowledge.

Sometimes we learned about pharmacies because of adverse events or other reports of problems. Our ability to pro-actively apply current good manufacturing practice (CGMP) standards to prevent problems is limited to pharmacies operating more akin to conventional manufacturers, yet our ability to examine records necessary to determine the scope or nature of a compounding operation during an inspection has been disputed. In addition, generally, compounding pharmacies are not required to submit adverse event reports or to label their products with information to help consumers and providers make more informed choices. Since the hearing, the newly enacted DQSA

when the product is used within a few hours, the risk of patient harm is significantly reduced. If product is shipped interstate, it may be held for a longer period of time before use, with a greater risk of contamination. In addition, there is a risk of inadequate state oversight of the compounding operation, because states have inconsistent standards for sterile compounding and apply varying degrees of resources and expertise to inspections and enforcement. The examples of nine separate incidents, where compounded products caused deaths and serious injuries, described in our testimony of May 23, 2013, illustrate the nature of the risk posed by inadequately controlled sterile compounding operations.

The production of a sterile drug with assured sterility is unavoidably complex, involving multiple steps and manipulations. Controlling the production process to ensure the integrity of the product is even more important when making a sterile product in larger volumes. Each process step could introduce an error or represent an opportunity for the introduction of microbial contamination into the finished product. Under FDA's CGMP regulations, manufacturers of sterile drug products are required to demonstrate that each manufacturing step has been validated to be suitable for achieving and maintaining sterility of the finished drug product, the entire process is performed under extremely high-quality environmental conditions, and there is a high state of control of the entire, integrated process as well as the facility in which sterile drug production is performed. Taken together, these controls result in a high level of assurance that a drug is sterile.

Based on our inspections, FDA learned that compounding pharmacies engaging in sterile compounding often engage in multiple manual manipulations of the product, increasing the risk of contamination. Contamination from operators is one of the more common sources of sterile drug product contamination. Manufacturers of FDA-approved drugs design sterile drug production lines to minimize exposure of the drug product to operators, often relying upon automated equipment that is more reliably sterilized and kept clean, reducing the possibility of contamination.

Considering all of these factors, compounding pharmacies do not have the same high level of sterile drug product quality assurance as manufacturers of FDA-approved drugs.

The Honorable Marsha Blackburn

The response to Question 1 below was e-mailed to Representative Blackburn's Health Policy Analyst on August 8, 2013.

1. **On the ANDAs, you said you prioritize those applications. How long does it take to get one of those through the process? Please elaborate.**

When a complete Abbreviated New Drug Application (ANDA) is submitted to FDA, it takes an average of three months to review it and take action.

Since the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, FDA has expedited the review of 44 ANDAs that have the potential to mitigate a drug shortage. Of those 44 ANDAs, seven included the components required to be considered complete and have actions associated with them. An action is either an "Approval," in which an approval letter is issued, granting the applicant permission to market the drug, or a "Complete Response," in which a complete response letter, or CR, is issued to the applicant, outlining the reasons why an ANDA cannot be approved in its present form. A CR provides information that an applicant can use to re-apply, but is considered a final action. Of the seven complete ANDAs that were expedited, two were approved, and five received CR letters.

Of the remaining 37 ANDAs expedited since FDASIA's enactment:

- Eight are for drugs that were recently added to the drug shortage list and are, therefore, newly expedited. These ANDAs are currently under review.

- Twenty-two will not be approved in their present form. The applicants will receive CR letters when all sections of the application are reviewed, so that all comments can be consolidated into one letter.

- Seven have received and submitted responses to FDA's CR letter, and their newly submitted information is under review.

More information on the ANDA approval process is available at *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm*.