FDLI Presentation
Outline

Good afternoon. I am here to talk with you a little about Public Citizen's perspective on pharmacy compounding, which is somewhat unique in that we are one of the only groups that have been pushing heavily for the FDA to step up enforcement of prior laws, rather than seek a legislative solution. I want to share a few examples of areas where we think the FDA could have done a better job with enforcement under the prior legal framework, as a way of framing what the future may hold for enforcement under the new legislation. And then I will talk a bit about some of the new concerns with implementation moving forward.

Unlike the FDA, we actually liked the prior legal framework set up by 503A, to the extent that it attempted to draw a line between traditional pharmacy compounding, which involves tailoring an individualized product for a specifically identified patient with a unique or unusual clinical need, and drug manufacturing, which involves mass-producing standardized products for a population that shares the a common set of clinical needs. An example of a need requiring traditional compounding would be a patient with an allergy to an inactive ingredient, such as peanut oil, in an FDA-approved drug, who needs a special allergen-free formulation.

While there were difficulties with the way 503A defined this line, we believe that the current legislative solution failed to solve these problems, and instead created a new third tier of companies, initially called "compounding manufacturers" but now called "outsourcing facilities," which will be permitted to mass-produce standardized drugs without FDA approval. We would characterize this activity as unapproved drug manufacturing, which was illegal under prior law.

The prior legal framework and FDA's enforcement under that framework offers us some insights into how compounding might be regulated under the new legislation.

Before the new legislation was passed, the FDA had two different mechanisms for defining traditional compounding and distinguishing it from illegal manufacturing of unapproved drugs: Section 503A of the FDCA, and its Compliance Policy Guide (CPG).

There were some key similarities between the CPG and Section 503A, and the new legislation leaves these key provisions largely intact. Two of the most challenging provisions are outlined here at the top:

1) A traditional compounder may engage in "anticipatory" compounding (i.e. making drugs before receiving a patient-specific prescription), only in "limited quantities," and
2) A traditional compounder may not make products that are "essentially copies" of FDA-approved products

The terms "limited quantities" and "essentially copies" are both subject to multiple interpretations, and the FDA has not developed a consistent policy defining or enforcing these standards, leaving them open to abuse by companies wishing to scale up operations and engage in manufacturing activity. The new law leaves in place 503A's definition of traditional compounding, while adding a third, voluntary category of "outsourcing facilities," who need not meet the 503A requirements, but instead must follow a distinct set of standards.

In spite of its limitations, we believe there is more that the FDA could be doing to apply this framework, and have some examples of that here.

The prime example is, of course, the New England Compounding Center (NECC). The CDC has estimated that close to 14,000 patients in 23 states received injections from just three lots of steroid manufactured by the NECC, a steroid that was available in an FDA-approved version.[1],[2],[3] This was clearly standardized, large scale production that should have been subject to enforcement under either 503A or the Compliance Policy Guide.

I have two other examples of cases of poor enforcement over the past decade: PharMEDium and Central Admixture Pharmacy Services, or CAPS.

Both pharmacies were associated with outbreaks in 2004-2005.[4],[5],[6] FDA responded in both cases by inspecting the implicated facility and identifying sterility problems and contaminated medication.

In each case, six months to two *years* after the inspections (a surprisingly long delay), the FDA issued a warning letter noting that each pharmacy was engaged in anticipatory compounding, describing sterility concerns, and accusing the pharmacy of making adulterated and misbranded drugs in violation of federal law.[7],[8]

Through a FOIA request, we learned that the FDA visited various CAPS and PharMEDium facilities over the few years following the letter, and found further sterility and quality concerns. These findings were never published and no warning letter ever issued.[9],[10]

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[1] http://www.cdc.gov/hai/outbreaks/infographic-read-access.html
[2] http://www.pfizer.com/files/products/material_safety_data/PZ01044.pdf
[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011757s085s086lbl.pdf
[4] http://www.washingtonpost.com/national/health-science/compounding-pharmacies-have-been-linked-to-deaths-illnesses-for-years/2013/02/07/5ba90132-6b19-11e2-ada3-d86a4806d5ee_story_2.html
[5] http://usatoday30.usatoday.com/news/health/2006-08-07-unsterile-families_x.htm
[6] https://www.premierinc.com/safety/public-health/downloads/cdc-advisory-serratia-03-18-05.pdf
[7] http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076357.htm
[8] http://www.fda.gov/iceci/enforcementactions/warningletters/2006/ucm075828.htm
[9] Inspection Reports on file with author.

Meanwhile, the FDA sent a letter to PharMEDium in 2005 stating that it would exercise agency discretion and broadly waive the requirement that PharMEDium seek individualized prior prescriptions for its products. Then, in 2007, the FDA investigated PharMEDium following another outbreak, this time involving eight patients in two states. However, the FDA could not confirm causation in this case because PharMEDium was not ensuring that hospitals kept track of which lot of drug the patients had received.[11],[12]

Many quality problems appear to be ongoing. Here were some of the problems the FDA found during inspections in 2013. These included:

In CAPS facilities:

- In a Massachusetts facility: failure to test all batches for sterility.[13]
- At a Connecticut site: cases of product contamination by the same species of *Staphylococcus* bacteria, with that bacteria also identified approximately 10 times within the facility during roughly the same period.[14]
- Various insects and pest reports.[15]

Then at aPharMEDium facility:

- "White and yellow residue" on HEPA air filters in the clean room[16]
- White particles on the floor in the clean room[17]
- Failure to test for sterility and potency.[18]

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[10] Inspection Reports on file with author.

[11] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM338614.pdf

[12] Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated with contaminated intravenous fentanyl. *Emerg Infect Dis* 2009;15(1):12-18.

[13] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348231.pdf

[14] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348237.pdf

[15] *Ibid.*

[16] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342277.pdf

[17] *Ibid*

We do not necessarily think that PharMEDium and CAPS are particularly bad actors for their industry. What we do think is that had the FDA been more aggressive about pursuing criminal and civil penalties against these and other companies when it identified problems, we would probably not have seen the same level of non-compliance in the industry that contributed to the NECC outbreak.

Looking forward, it's hard to say whether the FDA's enforcement approach will shift dramatically. The new statute will solve the problem of the Circuit split, which could help the FDA focus on developing a more consistent national standard for enforcement.

However, the statute preserves some of the most difficult challenges from the old framework, including the anticipatory compounding and essential copies language.

Companies may be reluctant to register as "outsourcing facilities" under the new framework and be subject to the federal requirements for outsourcers. One big question here is whether the FDA will allow outsourcers to manufacture unapproved drugs from a broad list of bulk ingredients, or limit their activity to just those ingredients that appear on the drug shortages list. Another big question is whether FDA will be aggressive about pursuing companies that fail to meet the 503A safe harbor, which in turn will encourage them to register as outsourcers.

Finally, we are quite doubtful that outsourcers can successfully be brought up to Good Manufacturing Practices standards without going through the new drug approval process and its accompanying assessments and inspections.

To give you an example of the scope of this task, I testimony from Bill Kennedy, a licensed pharmacist who founded a drug manufacturing company, Nephron Pharmaceuticals to seek out FDA approval for his products after the FDA threatened to prosecute his compounding pharmacy for illegal manufacturing in the early 1990s. It took Nephron six years to get its first FDA approval. By 2003, Nephron held just six generic drug approvals, but required compliance and quality control departments that contained 4 compliance officers, 41 quality assurance staff, 9 degreed chemists and 19 degreed microbiologists.

By contrast, we recently came across a press release from a compounding pharmacy in California advertising groundbreaking on its new "state of the art" facility, slated to open in just six months. The pharmacy, Leiter's, advertises compounding for over 11,000 "custom" prescription medications, and the president of the company is quoted in the press release saying: that the new facility will be at cGMP standards. Yet when I went to the company's website, I

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http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342277.pdf

learned that Leiter's employs just "two full-time quality control employees," and only one is a degreed pharmacist.[19]

Based on these figures, we are doubtful that Leiter's will actually be complying with cGMP, and we are doubtful that they can be made to comply through anything less than the new drug approval process.

I would like to close with a quote from Jeff Francer, a lobbyist for PhRMA, offered prior to the passage of the recent compounding legislation (and those of you familiar with Public Citizen's work will recognize that this is the first and could be the last time a PhRMA lobbyist is ever quoted favorably in a Public Citizen presentation):

> The same safety standards that govern biopharmaceutical manufacturing should also protect patients who are treated with medicines manufactured by large-scale compounders. . . . [W]e believe that an entirely new regulatory scheme is unnecessary to correct the enforcement issues surrounding the tragic NECC incident.

We agree. Ultimately, we believe that it was a mistake to create a new category of "outsourcing facilities" that need not seek new drug approval or comply with the same requirements as other drug manufacturers, and we hope the FDA keeps the scope of activity for these facilities limited. At the same time, the FDA should work within the framework of 503A to step up enforcement and clarify the line between compounding and drug manufacturing. We believe this is the only way to prevent a repeat of the NECC tragedy.

[19] http://www.leiterrx.com/quality-assurance/ Information collected October 22, 2013. (Note: as of December 18, 2013, the Leiters website had been updated and now describes "3 full-time employees dedicated to Quality Assurance").