Testimony before the Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
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The Pew Charitable Trusts

Dear Chairman Pitts, Ranking Member Pallone, and members of the Subcommittee,

Thank you for the opportunity to testify on the need for federal legislation to improve the safety of compounded medicines.

My name is Allan Coukell. I am a pharmacist by training and director of drug and medical device work at the Pew Charitable Trusts, an independent, nonpartisan research and public policy organization. Pew has a longstanding focus on drug quality issues.

This subcommittee and the Oversight Subcommittee have held a number of hearings on compounding, and have heard extensive testimony regarding the risks to patients.

I won't reiterate those risks today, except to say that the recent fungal meningitis outbreak that has killed so many Americans is far from an isolated incident. There have been plenty of other deaths and injuries caused by compounded drugs, and there is ample reason for ongoing concern about quality problems at compounding pharmacies.

Today I would like to propose ways that Congress can reduce these risks and at the same time ensure that patients have access to the medicines that they need.

Current law is inadequate for this purpose, both because legal decisions have created uncertainty about the status of section 503A of the Food Drug and Cosmetic Act, and because 503A does not recognize the emergence of large-scale compounding operations that are important for patient care yet far removed from traditional pharmacy practice.

Let me begin with two points that all stakeholders should endorse.

First, patients, doctors and pharmacists should prefer FDA-approved drugs over compounded medicines whenever possible.

Only FDA-approved drugs go through pre-market review to establish safety, efficacy and bioequivalence, as well as pre-approval of manufacturing methods and facilities.

Any new legislation must not encourage compounding at the expense of traditional manufacturing.

Second, the preparation of customized medicines in response to a prescription for an individual patient is an established part of pharmacy practice. This traditional compounding is a matter for state jurisdiction, and must remain so.

Now allow me to make a third point, which is that there is a large-scale compounding sector that fits neither of the above categories. Instead it undertakes batch production of products–often high-risk sterile products–and admixtures of FDA-approved drugs for use in hospitals and clinics.

Indeed, according to a recent report by the HHS Inspector General, 85% of hospitals that administer intravenous drugs purchase some of these products from outside pharmacies.[1] This is true for hospitals of all sizes, in some cases accounting for thousands of doses per day.

Pew recently joined with the American Hospital Association (AHA) and the American Society of Health-System Pharmacists (ASHP) to co-host a Pharmacy Sterile Compounding Summit.[2]

This meeting included representatives of hospitals of varying sizes, purchasing organizations, compounders, regulators, and pharmacy associations.

It also included experts in pharmacy practice and drug manufacturing quality standards. These experts emphasized the enormous difference between the standards developed for traditional pharmacy practice and the Good Manufacturing Practices that apply to drug manufacturing. They emphasized that only GMPs are adequate to ensure the safety of large-scale standardized production, and that USP compounding standards, which some have suggested could be used as a national standard, were developed for use in pharmacies and are therefore not suitable for larger-scale production.

cGMPs, on the other hand, are developed to ensure the proper production of large volumes of repeated batches of medicines which require standardized processes. These are the appropriate types of quality standards for large-scale compounding.

For example, cGMP requires manufacturers to validate systems and processes to ensure that medicines meet consistent quality and safety standards. Process validation becomes increasingly important as the same drug is compounded in repeat batches. In addition, USP 797 does not require the testing of a drug's starting ingredients, while cGMP does. And expiration dates are set for a manufactured drug based on extensive stability testing. But a beyond-use date for a

compounded medicine may in some cases be set by referencing published studies of drugs that may not conform exactly to the compounded product.[3,4]

Oversight of such standards is a role for the FDA, not for state boards of pharmacy.

Section 503A of the FDCA already recognizes the FDA's responsibility to oversee some compounding activities. 503A contains important elements to ensure that compounding not exceed traditional pharmacy practice, such as prohibiting the copying of marketed drugs. Importantly, it also gives the FDA the authority to create a list of drugs that may not be compounded.

However, merely reinstating section 503A would leave a lack of clarity about which facilities were subject to FDA oversight; moreover, it would not clearly give the FDA the ability to ensure that large-scale compounders comply with applicable GMPs.

Shutting down a facility or requiring an NDA may not always be in the public interest. As noted previously, a majority of hospitals now outsource some sterile production, repackaging, and admixture.

Drawing the line

Which facilities should be subject to GMP and therefore FDA oversight? It is a challenging line to draw, and there is no single ideal solution. A potential framework could build on the following factors:

- Volume of production. Clearly, larger-scale operations expose more patients to risks and are more amenable to the kinds of process measures that underpin GMP.
- Nature of the products. For example, sterile products, as a general matter, are higher risk than non-sterile (although the latter are not without risk) and sterile drugs manufactured from non-sterile precursors or bulk active ingredient are higher risk again than sterile repackaging or admixture that begins with FDA-approved sterile products.
- Percentage of sales. While an arbitrary sales threshold does not speak directly to risk, it is a potential mechanism that could help distinguish between traditional dispensaries that produce the occasional product and those whose business is based substantially on compounding.
- Expiry dates. Products used immediately or very soon after production are less likely to have undergone chemical decomposition or have sustained massive bacterial and fungal growth than products that sit on a shelf for a prolonged period beforeadministration. Extended beyond-use dating calls for higher production and testing standards and may also serve as a mechanism to distinguish between traditional pharmacy and something different.

- Interstate sales. The sale of products across state lines has been proposed as a mechanism to distinguish between state- and FDA-regulated operations. This would ensure that some large entities would be under FDA jurisdiction. It would provide a measure of regulatory clarity in that states would be entirely responsible for drugs produced within their own boundaries. However, it would leave some very large operations under state oversight and, conversely, would sweep into federal jurisdiction some very small facilities that make some interstate sales.

Finally, let me address the issue of the prescription. One thing that characterizes pharmacy practice is that pharmacies fill prescriptions. Any business whose principal activity is the production of products without a prescription is not a traditional pharmacy.

Some have suggested that compounding pharmacies should be allowed to retroactively reconcile the product they sell with a prescription received later. While such a requirement might serve to limit the scale at which a compounder operates, it is would not be sufficient to distinguish between traditional pharmacy and this new, large-scale sector.

Additional considerations

There are a number of additional elements to an effective proposal that we urge Congress to include. First, the FDA and compounders alike must clearly know which facilities are subject to FDA oversight. Such facilities should be required to register with the agency and, to avoid an unfunded mandate, pay a fee. Facility inspections should be periodic with their frequency based on a risk-based schedule and, following a transition phase, this should include an initial inspection before new facilities come online.

Under this framework, states may continue to require FDA-registered compounding facilities to hold state pharmacy licenses, but state enforcement of quality standards should be preempted for these facilities.

Legislation should be clear that a compounder may not make a copy or a variation of a marketed drug, except when that drug is in shortage or to address specific medical needs of a specific patient. Congress should also prohibit the wholesale of compounded drugs. All compounded medicines should be clearly labeled as such.

Another important safeguard against circumvention of the approvals process is limiting compounding from bulk to only well-characterized and already in-use active ingredients, such as those described by a USP monograph, or those in an existing drug application. These concepts are not new, but are part of current 503A language.

Key safety requirements should also be set at the federal level, such as a "do not compound" list. Congress has already recognized that certain products are not suitable for compounding (frequently cited examples include transdermal delivery systems, biologic products and sustained release formulations) and has given the FDA authority to establish a "do not compound" list. This authority should be maintained and should apply to both FDA-registered and non-registered facilities, as it does now.

In order to enforce these important provisions, the FDA needs to be able to inspect compounding pharmacies to know if they are complying with the law, and not just after patients have received contaminated drugs. Currently, the FDA has the authority to inspect all pharmacy compounders, and that authority should not be weakened. The FDA should not be limited in its ability to access a site to cases where a state has voluntarily notified the agency of a pharmacy violation. Furthermore, the FDA should be given the authority to inspect pharmacy records for purposes of enforcing the "do not compound" list.

Conclusion

We thank you for your leadership on this important issue. Congress has long recognized the role of the FDA in providing oversight of compounding. It is time to update the Food, Drug, and Cosmetic Act to remove ambiguities and create a clear, workable framework to address patient safety.

Thank you for the opportunity to testify, and I welcome your questions.

References

[1] Office of the Inspector General, Department of Health and Human Services. "Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them, OEI-01-13-00150". April 10, 2013. https://oig.hhs.gov/oei/reports/oei-01-13-00150.pdf

[2] Pharmacy Sterile Compounding Summit: summary of a stakeholder meeting. http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Other_Resource/Compounding_report.pdf

[3] United States Pharmacopoeial Convention. USP–NF General Chapter <797> Pharmaceutical Compounding—Sterile Preparations

[4] 21 CFR 211. Current good manufacturing practice for finished pharmaceuticals