Comments of the Pew Charitable Trusts

to the Senate HELP Committee

on S.959: the Pharmaceutical Compounding Quality and Accountability Act

June 7, 2013

Dear Chairman Harkin and Ranking Member Alexander,

Thank you for your continued bipartisan work on the safety of pharmaceutical compounding. We would like to provide additional comments to supplement our letter to the Committee of 22nd May.

Pew, the American Society of Health-System Pharmacists and the American Hospital Association recently hosted a "Pharmacy Sterile Compounding Summit" that brought together diverse stakeholders to assess the risks associated with sterile compounding. Based on the results of this conference our three organizations recommended clarifying oversight of sterile compounding, specifically by strengthening Federal oversight of activities that represent a higher degree of patient safety risk, and that are not currently overseen by States as traditional pharmacy compounding.[i]

The emergence of a high-volume compounding sector producing high-risk products necessitates an updated quality and oversight framework, including a reexamination of state and federal roles.

S.959 takes a step towards clarifying state and federal oversight of compounding, including an important increase in FDA supervision of certain activities: specifically, the compounding of sterile medicines that are shipped interstate. While we support this increase in oversight, we also urge the Committee to make key changes to further strengthen this bill.

Detailed Comments:

- **Compounding manufacturers (CMs) should be prohibited from making non-sterile medicines, or the FDA should be explicitly directed to oversee non-sterile compounding by CMs. (P.4 line 4)** The current bill directs the FDA to regulate compounding manufacturers (defined as facilities that make sterile products in anticipation of a prescription and ship them interstate) but does not address compounding of non-sterile products by compounding manufacturers. Since CMs are expressly prevented from being state-licensed pharmacies, this leaves a lack of clarity on quality standards and regulatory oversight. To achieve clarity, the legislation should either expressly require FDA to oversee non-sterile compounding at CMs or prohibit CMs from making non-sterile medicines.

- **Ensure that state-licensed pharmacies operating as traditional compounders (TCs) do not become de facto unregulated manufacturers by defining anticipatory compounding. (P.8 line 24)** The threshold for allowable anticipatory compounding by TCs is a longstanding area of confusion. The terminology used in section 503(A), as well as this bill, permits anticipatory

compounding in "limited quantities" based on prescribing history. FDA's compliance guide allows "very limited quantities". These terms are undefined, and are interpreted in widely different ways by different stakeholders. The definition of a traditional compounder in this legislation includes compounding limited amounts in anticipation of a prescription pursuant to state law, which by some assessments also permits compounding without a prescription (aka office stock or hospital supply) where allowed by states.

While some states may limit office-stock compounding, others may not. This would allow TCs to manufacture unlimited quantities of medicines. To ensure that state-licensed pharmacies operating as TCs do not become de facto unregulated manufacturers, clear limits on the amount of compounding permitted in anticipation or without a prescription should be established. To ensure clarity and enforceability, Congress should (1) direct FDA to establish volume thresholds for compounding in anticipation of / without a prescription through regulation, and (2) clarify that this is a uniform federal standard not pursuant to state law.

Alternatively, if a clear federal standard is not established, compounding in anticipation or without a prescription should be regulated by States. However, this would undermine the protections established through the FDCA and put patients at risk from drugs made by unregulated manufacturers.

- **Provisions regarding making a copy or variation of a marketed drug should be clarified.**
    - **The term "variation of a marketed drug" must be defined. (P.12 line 25)** Compounding a product from API appears to be permitted under this proposal, but compounding a *variation of a marketed drug* from API is subject to strict limits. However, the proposal does not define "variation of a marketed drug", making it unclear what activities are subject to these limits.
    - **Clarify whether CMs may make variations of a marketed drug from bulk ingredients. (P.16 line 23 – p.17 line 7)** The current language is unclear. It permits compounding a variation from bulk if a practitioner determines a clinical difference and if *a TC* receives a prescription in advance, but there is no language affirmatively permitting or prohibiting compounding manufacturers from this activity.
    - **To make a variant of a marketed product from bulk ingredients, a TC must receive a prescription in advance that states that the product needs to be compounded. (P.17 line 7)** This would be a stronger provision than current language requiring the prescription to state the product *may* be compounded.
- **Do not require compounding manufacturers to notify the FDA 14 days prior to compounding a copy of a marketed drug in shortage. (P.18 line 1)** The FDA should be notified when a compounder makes a copy of a drug in shortage, but 14 day advance notification, as the bill appears to require, is an unreasonable expectation when companies are reacting to emergent shortage situations. We support the provisions requiring compounding manufacturers to register with the FDA as an entity that intends to compound shortage drugs and the inclusion of

such indication as criteria for risk-based inspections. In this way FDA will be able to provide early oversight to ensure quality at the facility. We also support the intent of the current language that permits compounding and distribution of a copy of a marketed drug *only* when that drug is on FDA's drug shortage list. However, we note that additions to, and removals from, the FDA shortage list may lag real-world conditions and do not reflect local conditions, given that products may be in shortage in some regions and available in others.

- **Compounding manufacturers should be allowed to repackage biologics without receiving specific patient names in advance. (P.20 lines 5-12)** The CM category recognizes that this sector may compound (including repackage) without a prescription, but prohibits repackaging of biological drugs unless a CM receives a medical order with specific patient names. While a prohibition on the creation of biological products from bulk ingredients makes sense, given their complexity, we are unaware of a scientific rationale to limit a CM's ability to repackage these products for office or hospital stock, as they are permitted to do for small molecule drugs under this proposal. Sterile repackaging for all drugs should be done under applicable GMPs, which will include the determination of stability and sterility. It would be undesirable to drive biologic repackaging away from GMP-compliant CM facilities and into the doctor's office by limiting CMs to patient-specific repackaging.

  Finally, a medical order with patient names is undefined, and there may be arguments additional against a CM receiving specific patient names as they are not allowed to register as pharmacies and therefore are not state-enforced pharmacy standards such as proper patient information protection.

- **Require any healthcare facility or practitioner ordering products from a CM to state on the order that a compounded drug is needed. (P.27 line 9)** A health care facility or practitioner's intent to purchase a compounded product to have in stock must be affirmatively stated on ordering documentation. Because CMs are producing medicines outside of an assessment of individual patient need for a compounded product, there must be alternate systems to ensure that the purchasing health care entity or practitioner is explicit that a compounded product is needed. This will support the important concept of a practitioner determining clinical need, and will ensure that someone with direct responsibility for the patient's care always knows that the medicine is not an FDA-approved drug.

- **Define "under direct supervision of a pharmacist". (P.27 line 14)** It should be clear that the pharmacist directing production of these medicines is legally responsible for adherence to applicable laws and standards, and liable for quality failures.

- **TCs should also be required to label their drugs as "compounded drugs." (P.37 lines 5-12)** Traditional compounders will already be required to label compounded medicine as "not for resale." It does not make sense to exclude them from a requirement to also state that a medicine is a compounded drug.

- **Allow the FDA to access records during inspections of all pharmacies, not just CMs. (P.52 lines 14-20)** This proposal sets federal standards for traditional compounding, such as a federal

do-not-compound list, which FDA must have investigative tools to enforce. Further, if the agency is responsible for oversight of compounding manufacturers, it must have the ability to determine whether a facility meets the enumerated criteria (sterile, anticipatory, or interstate compounding). It is impossible to assess the latter two criteria without access to records.

- **Consider allowing alternate models of joint federal and state jurisdiction for entities that wish to engage in compounding manufacturing and pharmacy practice**. We would support allowing a CM to also be a licensed pharmacy and therefore subject to relevant state pharmacy law. It could be clear that the FDA's authority is specific to the oversight of sterile manufacturing. Any entity that engages in pharmacy practice must be licensed as a pharmacy and subject to State oversight.

In addition to these comments, we are compelled to reassert that S.959 would bring just one segment of the compounding industry clearly under FDA oversight and appropriate quality standards. The legislation does not address other high-risk compounding activities, such as large-scale, *intra*state sterile compounding and large-scale *non*-sterile compounding. Indeed, by reducing FDA's authority over certain state-regulated pharmacies (as discussed above), the law may encourage the growth of these types of compounding.

Thank you again for your commitment to improving the safety of the U.S. drug supply by addressing gaps both our drug distribution security system and the oversight of pharmacy compounding. Moving forward, we urge you to continue to improve this legislation to ensure a clear, workable regulatory framework that will result in a net improvement in patient safety.

[i] The Pew Charitable Trusts, the American Society of Health-System Pharmacists, and the American Hospital Association. "Pharmacy Sterile Compounding Summit: Summary of a Stakeholder Meeting". April 2013. http://www.pewhealth.org/other-resource/safety-problems-at-compounding-pharmacies-confirm-need-for-better-oversight-85899468188