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May 3, 2013

The Honorable Tom Harkin
Chairman
U.S. Senate Committee on Health, Education, Labor, and Pensions
731 Hart Senate Office Building
Washington, DC 20510

The Honorable Michael B. Enzi
Ranking Member
U.S. Senate Committee on Health, Education, Labor, and Pensions
379A Russell Senate Office Building
Washington, DC 20510

Re: Public Citizen's Comments Regarding the Senate HELP Committee Draft Legislative Proposal for Regulatory Oversight of Compounding Pharmacies

Dear Senators Harkin and Enzi:

Thank you for the opportunity to provide comments regarding U.S. Senate Committee on Health, Education, Labor, and Pensions (HELP Committee) draft legislative proposal for regulatory oversight of compounding pharmacies.

Public Citizen, a consumer advocacy organization representing more than 300,000 members and supporters nationwide, wishes to express grave concerns with the Committee's draft legislative proposal, which will endanger public health by threatening to worsen the very quality and safety problems it seeks to address. Our detailed comments are enclosed.

The HELP Committee proposal does not strengthen existing laws governing pharmacy compounding. Instead, the proposal would weaken existing laws governing drug manufacturing by legalizing an entirely new regulatory class of drug manufacturers that would be subject to substandard requirements for ensuring the efficacy, safety, quality, and labeling of drugs.

Public Citizen believes that better legislative proposals are possible that would, among other things, strengthen the Food and Drug Administration's (FDA's) authority to police the line between traditional compounding and drug manufacturing by requiring compounders to register

with the FDA and granting the FDA authority to fully inspect traditional compounding pharmacies, regardless of whether they engage in drug manufacturing activities.

Again, thank you for the opportunity to comment on this important public health matter. Please feel free to contact us if you have any further questions or require our assistance.

Sincerely,

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Public Citizen's Health Research Group

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Enclosure



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Public Citizen’s Comments Regarding Senate HELP Committee Draft Proposal on Pharmaceutical Compounding

May 2013

Executive Summary

Public Citizen opposes the draft legislation on pharmacy compounding released Friday, April 26, 2013, by the U.S. Senate Committee on Health, Education, Labor, and Pensions (the Senate HELP Committee). The legislation would dramatically weaken patient protections by creating a dangerous new class of drug manufacturers, confusingly called “compounding manufacturers.” This proposed class of drug manufacturers would be distinct from “traditional compounders,” which would be fully exempt from federal authority under the proposed statute.

We are in favor of a statute that would create a clear line between traditional compounding and drug manufacturing and define federal and state authority with regard to each.¹ Yet the proposed bill does not do this. Instead, the draft legislation creates a third group: drug manufacturers described as “compounding manufacturers.” This new proposed class would be legally permitted to mass-produce standardized drugs and sell them across state lines without obtaining Food and Drug Administration (FDA) approval or meeting the federal requirement that the drug’s labeling include adequate directions for use — requirements currently mandated for all drug manufacturers.

Rather than strengthening the FDA’s authority over high-risk manufacturing activities, this bill would eliminate important federal requirements that protect patients from unsafe and ineffective drugs, and it would bring about massive deregulation of a growing industry of second-tier drug manufacturing that has been permitted to thrive under the guise of “pharmacy compounding,” in violation of current federal law. Even worse, the substandard drugs manufactured by proposed second-tier “compounding manufacturers” would carry no warning label to notify hospitals, doctors and patients that drugs made by this industry are not approved by the FDA or evaluated by the agency for safety, efficacy, and accurate labeling.

Under current law, compounding pharmacies that mass-produce standardized products, as opposed to producing customized drugs to meet an individual patient’s needs, are drug manufacturers subject to FDA regulation. As manufacturers, these firms are required by law to submit a premarket approval application to the FDA prior to bringing a new drug onto the market. Such applications must document that the new drug is safe and effective, either by running extensive human clinical trials (in the case of a brand-name drug), or by establishing bioequivalence with an existing FDA-approved drug (in the case of a generic drug).

¹ Traditional compounding is preparation by a pharmacist of an individually customized drug, in response to a physician’s prescription, for a patient with unique medical needs that cannot be met by a commercially available, FDA-approved drug manufactured by a pharmaceutical company.

In the past, the FDA has been slow to enforce federal laws against companies calling themselves “compounding pharmacies,” even for cases in which the companies clearly were engaged in manufacturing activity subject to federal law.

Yet rather than pushing the FDA to fully use its existing authority and giving the agency enhanced authority to monitor and inspect all compounding pharmacies, the Senate HELP Committee proposal ratifies and endorses the FDA’s history of under-enforcement, allowing “compounding manufacturers” to continue manufacturing drugs under greatly weakened federal standards.

Under these weakened standards, “compounding manufacturers” could mass-produce new dosages, formulations, and even (in some cases) new active ingredients without obtaining FDA premarket approval or complying with federal labeling requirements.

Moreover, the proposed bill fails to strengthen federal oversight over traditional compounding, ensuring that the FDA will continue to experience problems policing the line between traditional compounding and drug manufacturing for pharmacies that do not qualify for the “compounding manufacturer” exemption.

Such massive deregulation is not warranted to address the medical needs of patients. We urge the HELP Committee to set aside this flawed legislative proposal and draft a new proposal that:

- Draws a clear line between traditional compounding and drug manufacturing, with no category of second-tier, substandard drug manufacturers, such as the so-called “compounding manufacturers.”
- Provides adequate funding to the FDA to aggressively enforce existing laws against “compounding pharmacies” that cross the line into manufacturing.
- Strengthens the FDA’s authority to police the line between traditional compounding and drug manufacturing by requiring compounders to register with the FDA and granting the FDA authority to fully inspect traditional compounding pharmacies, regardless of whether they engage in drug manufacturing activities.
- Strengthens the FDA’s ability to prevent dangerous compounding of specific high-risk drugs by giving the FDA authority to identify withdrawn products, dosage forms, and active ingredients that cannot be compounded.
- Requires clear, standardized warning labels to communicate to providers and patients who purchase traditional compounded products that the safety, efficacy, and accuracy of the product’s labeling have not been assessed by the FDA.

I. The HELP Committee’s Current Proposal Would Weaken Important Federal Requirements.

Drug-approval and labeling requirements are central to the federal system of drug regulation and cannot be weakened without severely compromising the safety and quality of our nation’s drug supply. First and foremost, the requirements mandate that manufacturers test each dosage² and formulation of each active ingredient to ensure that the end product is safe and effective prior to marketing.³ This process is

² In the case of generic drugs, however, the drug’s sponsor may not be required to confirm bioequivalence for every dosage strength to obtain approval to market multiple doses.

³ 21 U.S.C. § 355.

resource-intensive but yields critical information about the appropriate uses for the end product, including potential side effects, high-risk populations, issues with how the body absorbs or metabolizes the drug, appropriate conditions of use, and interactions with other products. The FDA can also require post-market testing if a potential new safety risk is poorly understood and requires further research.⁴

Premarket approval not only ensures the collection of important safety and efficacy data but also establishes the FDA as a gatekeeper for quality control. Prior to approving a drug, the FDA requires a detailed description of the manufacturing processes used during production, along with data from tests validating that these processes are sufficient to ensure the purity, potency, and consistency of the end product. If the agency has any concerns about the application or the sponsor, it may conduct a pre-approval inspection to verify the accuracy and authenticity of the data submitted in the application and confirm that the facility is following federal standards known as “good manufacturing practices” (GMP) with regard to that product.⁵

Finally, the new drug approval process and federal labeling regulations require that the manufacturer develop and the FDA review and approve the drug’s label to ensure that instructions for use are adequate and include all important safety and efficacy information obtained through clinical testing. Physicians making decisions regarding use of a drug rely on the information in these labels, including the indications for use, precautions and warnings about serious toxicities, and contraindications for use. The FDA can deny a new drug approval if the claims made in the drug’s labeling are not supported by evidence from adequate animal and human testing, or if important safety risks are excluded from the label.⁶ The FDA also relies heavily on the federal labeling requirement to prosecute manufacturers for making “off-label” efficacy claims that are not supported by the evidence.

The proposed law eliminates these important provisions for “compounding manufacturers,” effectively gutting a substantial portion of the federal regulatory regime for this new, second-tier, less regulated class of drug manufacturers. Without these provisions, a “compounding manufacturer” could mass-produce new drug formulations, combinations, and even active ingredients⁷ that have not been evaluated for safety and efficacy. It could launch new, untested manufacturing processes without first receiving an inspection or approval by the FDA, and it could include directions for use involving new, untested indications not evaluated by the FDA or supported by adequate data generated from clinical testing.

In place of new drug approval and labeling requirements, the draft legislation proposes several safeguards to control products that may be made by traditional compounders or “compounding manufacturers.” Though some of these safeguards may be helpful in controlling some of the worst abuses and may be appropriate tools to assist the FDA in limiting dangerous activity by traditional compounders, none serve as adequate replacements for the pre-market approval system for manufactured drugs.

⁴ 21 U.S.C. § 355 (o).

⁵ US Government Accountability Office. Drug Safety: FDA has conducted more foreign inspections and begun to improve its information on foreign establishments, but more progress is needed. GAO-10-961. September 2010.

⁶ 21 U.S.C. § 355(d); 21 C.F.R. § 201.56.

⁷ Provided the active ingredient is listed in the United States Pharmacopeia (USP). However, the USP does not require safety and efficacy testing prior to listing a drug, making it a poor substitute for FDA approval.

The bill would authorize the FDA to identify active ingredients or dosages and formulations that should not be compounded by using one of several “do not compound” lists.⁸ With regard to labeling claims, the bill would require “instructions for use, as appropriate.”⁹ The FDA could also prosecute a compounding manufacturer under existing provisions of the federal Food, Drug, and Cosmetics Act (FDCA) for false or misleading statements in a drug’s labeling, or labeling instructions that render the product dangerous to health.¹⁰

The problem with these safeguards is that they can only be used after the FDA has received information that a drug presents a safety risk. The FDA is likely to list a drug as “do not compound” only if there is evidence, obtained after patients’ use, that the active ingredient or dosage and formulation is especially dangerous. Similarly, the FDA cannot meet the burden of proving that a labeling statement failed to contain “appropriate” instructions for use, was false or misleading, or rendered the product dangerous, without evidence that the drug is unsafe or ineffective. Accordingly, the FDA will not be able to take action in most cases until after it has received evidence that patients have been injured or killed by a product marketed on a large enough scale to harm numerous patients. At worst, the FDA will never take action, because some risks can only be clearly identified through clinical testing, which the FDA cannot require except as a condition of new drug approval.¹¹

II. The Proposal Would Not Strengthen Federal Oversight of Traditional Compounding Pharmacies.

The proposed legislation fails to accomplish its purpose of clarifying the line between drug manufacturing and traditional compounding. Traditional compounding involves preparation by a pharmacist of an individually customized drug, in response to a physician’s prescription, for a patient with unique medical needs that cannot be met by a commercially available, FDA-approved drug manufactured by a pharmaceutical company. This individualized tailoring of medicines, when limited to its traditional scope, serves an important public health function and should not be eliminated. Instead, it should be appropriately regulated by state boards of pharmacy, with a much more limited role for federal oversight.

Yet in recent years, certain companies calling themselves “compounding pharmacies” have engaged in activities that far exceeded the traditional practice of compounding, carrying out large-scale production of standardized products, often substandard copies of FDA-approved drugs. Much of this activity clearly constitutes drug manufacturing subject to regulation by the FDA. Yet too often, the FDA has failed to act swiftly and aggressively against these companies. FDA officials have pointed to “gaps and ambiguities” in current law to explain the FDA’s failure to take enforcement against these compounding

⁸ Draft Proposal on Pharmaceutical Compounding. HELP Draft for Stakeholder Discussion. April 26, 2013. page 7, lines 3-7, 12-16; page 16, lines 4-22.

⁹ Draft Proposal on Pharmaceutical Compounding. HELP Draft for Stakeholder Discussion. April 26, 2013. page 20, lines 20-21.

¹⁰ 21 U.S.C. § 352(a), (j).

¹¹ Absurdly, the restrictions on drugs used in food-producing animals are much stricter under the proposed bill: an animal drug may not be compounded from bulk active ingredients unless the FDA specifically lists the active ingredient on a list of drugs that can be compounded. Draft Proposal on Pharmaceutical Compounding. HELP Draft for Stakeholder Discussion. April 26, 2013. page 15, lines 1-7.

pharmacies engaged in drug manufacturing.¹² These “gaps and ambiguities” primarily relate to difficulties in defining the line between traditional compounding and drug manufacturing.¹³

While these challenges do not present insurmountable barriers to FDA enforcement, they make enforcement more expensive. For example, the current section 503A of the FDCA (which remains in force in some parts of the country), creates an “advanced compounding” exemption that allows pharmacies to compound drugs “in limited quantities” before receiving a prescription order for an individual patient, if such compounding is based on a “history” of similar orders. To prosecute a pharmacy that claims this advanced compounding exemption, the FDA must expend significant resources to gather facts and build a case that the pharmacy has gone beyond making “limited quantities” and engaged in mass-production.

Pharmacies also sometimes attempt to evade FDA inspectors by denying that the FDA has authority to inspect their records.¹⁴ To inspect a pharmacy that contests the FDA’s authority, the FDA must obtain a warrant showing that the “pharmacy” is engaged in drug manufacturing and therefore not exempt from federal authority.

In addition, the FDA also may not have clear authority to stop truly traditional compounding pharmacies from selling dangerous formulations, dosages, or active ingredients — even if the dose, formulation, or product has been denied approval or withdrawn from the market because it is unsafe or ineffective.¹⁵

Sadly, the draft legislation would not expand FDA authority to address these challenges. Rather than clarifying or eliminating the advanced compounding exception, the draft would maintain the advanced compounding provision as is and add a *new* broad exception for hospital pharmacies, which will be exempt from all FDA oversight even if they mass-produce standardized drugs and ship them interstate.

¹² Statement of Margaret Hamburg, M.D., Commissioner of Food and Drugs, before the Subcommittee on oversight and investigations committee on energy and commerce, U.S. House of Representatives. April 16, 2013.

¹³ In areas of the country where 21 U.S.C. § 503A remains in effect, this line is defined by statute. In other areas of the country, the FDA had discretion to permit traditional pharmacy compounding. FDA Compliance Policy Guide § 460.200. Some courts may also find an implied statutory exemption for purely traditional practices under the Food, Drug, and Cosmetics Act. *See Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

¹⁴ *See* 21 U.S.C. § 360(g) (exempting from records inspection authority those pharmacies “which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice”).

¹⁵ The current section 503A authorizes the FDA to generate a list of drugs that may not be compounded because they have been withdrawn from the market as unsafe or ineffective. However, section 503A is no longer enforceable in some parts of the country, and in these regions the FDA’s authority over truly traditional compounding remains unclear. Moreover, even if it were enforceable, the current 503A does not address formulations or active ingredients that should not be compounded because they are especially difficult to compound, nor does it prevent traditional compounders from making drugs from active ingredients that the FDA declined to approve due to concerns about safety and efficacy.

In addition, the bill would not give the FDA needed authority to inspect the records of traditional compounding pharmacies. Instead, the bill would authorize the FDA to inspect compounding manufacturers — many if not all of which are already subject to the records inspection provision of current law because they are engaged in drug manufacturing. Without clear authority to inspect records, the agency will face difficulties when it encounters a “pharmacy” that has attempted to shelter its drug manufacturing activities under the exemption for traditional compounding. Such “pharmacies” could include those that mass-produce non-sterile products, as well as those that produce sterile drugs and sell them within the same state.

III. Deregulation Is No Solution

The deregulation proposed by the draft legislation is not warranted to address drug shortages or to supply hospitals and clinics. Temporary shortages of FDA-approved drugs should be addressed by the FDA working in partnership with the sponsors of FDA-approved drugs. Any needs resulting from shortages should not be met by authorizing second-tier drug manufacturing.

Moreover, shortages of FDA-approved drugs would be more likely to become permanent if demand for the FDA-approved product is diverted to cheaper compounded versions, which would be a predictable outcome under the HELP Committee’s proposed legislation. The provisions within the proposed legislation intended to safeguard against such competition would be difficult to enforce and contain substantial loopholes. These provisions make it illegal to market a drug that is a copy or variation on an FDA-approved product, unless that product appears on the FDA drug shortages list or a pharmacy obtains a prescription order “indicating that the compounded variation produces for that patient a significant difference.” We have serious doubts that these provisions can be adequately enforced and believe there will be substantial transaction costs for the sponsor of an FDA-approved drug seeking to re-enter a market that has been saturated by compounding manufacturers during a drug shortage.

More importantly, even if these provisions were adequately enforced, they would not eliminate competition that occurs when a compounded product with a different active ingredient is substituted for an FDA-approved product indicated to treat the same condition, a practice that will be difficult to track or control.

In some cases, the needs of hospitals and other health care providers may be met through compounding services that go beyond the scope of traditional compounding. In many cases, these needs can also be met by purchasing FDA-approved products made by traditional drug manufacturers. Yet providers may prefer to buy compounded products for reasons of cost, convenience, or treatment preferences that are not based on scientific evidence. There may be some additional limited category of medical needs that cannot be met either through traditional compounding or by purchasing an FDA-approved product. Yet if these needs exist, they can be better addressed through more targeted laws — for example, by an exemption for mixing an FDA-approved product in accordance with the drug’s FDA-approved labeling. These limited needs do not justify creating a sweeping second tier of “compounding manufacturers” operating under weakened federal standards.

IV. Conclusion

We urge the HELP Committee to set aside this flawed legislative proposal and develop a new draft that incorporates the five points stated on page 2, above.