PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

November 2, 2012

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: Questions for Stakeholders Regarding Appropriate Regulation of Pharmacy Compounding

Dear Senators Harkin and Enzi:

Public Citizen, representing more than 300,000 members and supporters nationwide, appreciates the opportunity to respond to the questions regarding pharmacy compounding that were posed by the Senate Committee on Health, Education, Labor, and Pensions (HELP Committee). Please find enclosed our responses to these questions.

The now widely publicized outbreak of life-threatening fungal meningitis in back-pain patients linked to contaminated steroid injections prepared by the New England Compounding Center, a compounding pharmacy located in Massachusetts, highlights the failure of the Food and Drug Administration's (FDA's) regulatory oversight of drugs prepared and sold by such pharmacies.

What is particularly tragic for the families of those who have been sickened or killed by the tainted steroid drug is that this situation was completely avoidable given the FDA's current legal authorities. Indeed, over the last decade, the FDA has been remarkably consistent and unwavering in asserting that the agency has legal authority over compounding pharmacies, particularly those that engage in drug manufacturing through the large-scale production and distribution of standardized versions of drugs.

The HELP Committee and other congressional committees responsible for overseeing the activities of the FDA should fully investigate the role this agency, as well as others, played in allowing the meningitis outbreak to occur. This investigation must identify all FDA officials whose actions and decisions contributed to the agency's failure to prevent this public health catastrophe. Ultimately, the senior leadership within the Office of the Commissioner, the Center for Drug Evaluation and Research, and the Office of Chief Counsel must be held accountable.

The Congress should await the completion of its investigations before deciding what legislative measures are needed to enhance the regulatory oversight of compounding pharmacies.

Please feel free to contact us if you have any further questions or would like our assistance.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

Enclosure

PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Public Citizen's Responses to Senate HELP Committee
Questions for Stakeholders Regarding Appropriate Regulation of Pharmacy Compounding
November 2, 2012

Current Authorities:

- What state or federal laws or regulations could have and should have been used to prevent the New England Compounding Center tragedy from happening?

  Public Citizen's Response: The Food and Drug Administration (FDA) obviously plays the central role at the federal level in the regulatory oversight of compounding pharmacies. Since the Federal Food, Drug, and Cosmetic Act (FDCA) was enacted in 1938 and subsequently amended in 1962, giving the FDA the authority to ensure that all brand name and generic drugs were both safe and effective, respectively, the FDA has had authority over all producers of drug products shipped in interstate commerce or composed of ingredients shipped in interstate commerce, including compounding pharmacies.

  Over the last decade, the agency has been remarkably consistent and unwavering in acknowledging and asserting that the agency has the legal authority over compounding pharmacies, particularly those that engage in drug manufacturing through the large-scale production and distribution of standardized versions of drugs, such as the New England Compounding Center (NECC), the compounding pharmacy at the center of the ever-expanding fungal meningitis outbreak.

  The enclosed appendix provides pertinent excerpts from a small sample of policy documents and letters issued by the FDA between 2002 and 2012, confirming and articulating the agency's regulatory authority over compounding pharmacies. These letters cite pertinent provisions of the current FDCA that were being violated by numerous compounding pharmacies.

  For example, on December 4, 2006, the FDA issued warning letters to the NECC and four other compounding pharmacies, directing them to stop producing standardized versions of medications that, according to the agency, were being "marketed for general distribution rather than responding (sic) to the unique needs of individual patients."[1]

[1] The Food and Drug Administration. FDA Press Release: FDA Warns Five Firms to Stop Compounding Topical Anesthetic Creams. December 5, 2006. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108793.htm. Accessed November 2, 2012.

The NECC was then cited for numerous alleged violations of the FDCA related to marketing four different drugs, including repackaged doses of the cancer drug Avastin into syringes that could be used for injection into the eye.[2] (Avastin is used off-label to treat macular degeneration).[3]

Clearly, in this instance six years ago, the FDA considered the NECC and the other compounding pharmacies to be engaged in drug manufacturing. The pharmacies, like any other drug manufacturer, were subject to the safety and effectiveness standards required for approval of new drugs, as well as the rigorous manufacturing standards designed to ensure that drugs are sterile and uncontaminated with such germs as bacteria or fungi before being sold and distributed.

However, following its December 4, 2006, warning letter to the NECC, the FDA subsequently dropped the ball and failed to take the subsequent actions necessary to ensure that the NECC adhered to these drug standards, which are essential for protecting the health of patients. For whatever reason, whether inattentiveness, lack of resources, or other reason, the FDA allowed the NECC to continue its wide-scale manufacturing and interstate distribution operation of multiple injectable drugs.

Also at the federal level, the Centers for Medicare and Medicaid (CMS), through its reimbursement policies concerning compounded drugs, has probably created inadvertent incentives for inappropriate use of compounded drugs, allowing large-scale drug production by compounding pharmacies to flourish. The CMS clearly has authority to deny Medicare payment for compounded drugs produced in violation of the FDCA. The agency used this authority in 2007 to deny coverage for inhaled drugs administered with nebulizer devices. In making that coverage decision, the agency concluded that compounded versions of multiple inhaled drugs administered via nebulizer did not meet the legal standard of being "reasonable and necessary."[4] As a result of this action, the wide-scale production of compounded inhaled drugs markedly dropped. The rationale used for this denial of coverage was applicable to many other compounded drugs being produced on a large scale by compounding pharmacies, but CMS has failed to use this authority consistently.

Finally, though the state of Massachusetts has regulatory authority over the NECC through the Massachusetts Board of Registration in Pharmacy, state regulations alone likely could not have prevented the NECC tragedy. The Massachusetts Board has the authority to inspect the NECC's facilities and could have taken action to suspend or terminate the company's state pharmacy license years ago. However, the NECC, while located in Massachusetts, apparently was licensed in all 50 states and the District of

---

[2] FDA Warning Letter: New England Compounding Center, December 4, 2006. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076196.htm. Accessed November 2, 2012.

[3] Pollack A, Avastin injections are reported to cause blindness. *The New York Times*. August 30, 2011.

[4] Noridian Administrative Services (Durable Medical Equipment MAC). Local Coverage Determination (LCD) for Nebulizers (L11488). Available at https://www.noridianmedicare.com/dme/coverage/docs/lcds/current_lcds/nebulizers.htm%3f. Accessed November 2, 2012.

Columbia and distributed thousands of different drug products across the country. The company thus was engaged in interstate commerce. While each individual state had regulatory authority over the NECC to varying degrees, such wide-scale drug production and distribution requires federal oversight to ensure patient safety.

- To what extent, if any, does legal uncertainty regarding the status of section 503A of the Food, Drug and Cosmetic Act (FDCA) affect oversight of pharmacy compounding?

  Public Citizen's Response: The FDA concluded that 503A of the Food and Drug Administration Modernization Act of 1997 (FDAMA) was invalid in its entirety throughout the country following the U.S. Supreme Court's decision in 2002 in *Thompson v. Western States Medical Center et al*, 535 U.S. 357 (2002), invalidating the advertising provisions under the First Amendment.[5] The FDA's conclusion that the entire act was invalid was based on a decision by the Ninth Circuit Court of Appeals ruling that the advertising-related provisions of section 503A were not severable from the section's unconstitutional advertising provisions.[6] The Supreme Court did not review the Ninth Circuit's ruling on severability, therefore leaving the ruling in place and invalidating all of section 503A.

  Based on its conclusion, the FDA issued revised guidance in May 2002 reaffirming its long-standing legal authority over compounding pharmacies and its intent to continue to use "enforcement discretion" by not taking compliance action for violations of the FDCA against those compounding pharmacies engaged in the traditionally narrow role played by such pharmacies. This narrow role involves purchasing bulk active ingredients from an FDA-registered drug manufacturer and reprocessing the ingredients, in response to physicians' prescriptions, into individually tailored preparations of drugs for patients with unique medical needs that cannot be met by a commercially available standard drug manufactured by an FDA-registered pharmaceutical company. In that same guidance, the FDA stated that those compounding pharmacies that engage in manufacturing and distribution of unapproved new drugs on a wide scale would be subject to enforcement actions for violations of the FDCA.

  Thus, the FDA did not consider there to be any legal uncertainty regarding its authority over entities that engage in drug manufacturing under the guise of a compounding pharmacy.

- Do current pharmacy licensing standards address compounding standards? Do those laws need to be clarified to ensure accountability?

  Public Citizen's Response: Public Citizen has not formally reviewed the current pharmacy licensing standards for all states. We would anticipate significant variability

[5] Food and Drug Administration. Compliance Policy Guidance Section 460.200: Pharmacy Compounding. Reissued May 29, 2002. *Available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm

[6] *Ibid.*

in these standards across states. There likely is a need for a federal law that sets minimum safety and quality standards for all drugs prepared by compounding pharmacies engaged in the traditional narrow role of such pharmacies, as described above. Such requirements are particularly necessary because states have a limited ability to protect their residents from drugs compounded in other states under weaker regulatory standards.

FDCA 503A:

- Should Congress clarify the legal status of section 503A given the current split between 9th and 5th Circuits? If so, should section 503A be formally enacted again without the unconstitutional advertising provision?

  Public Citizen's Response: As stated above, it is Public Citizen's position that the current provisions of the FDCA provide the FDA with the necessary authority to regulate compounding pharmacies that, like the NECC, engage in large-scale production and distribution of standardized drugs.

  The Fifth Circuit's decision in *Medical Center Pharmacy v. Mukasey,* 536 F.3d 383 (5th Cir. 2008), does not prevent the FDA from regulating compounding pharmacies that engage in large-scale production and distribution of standardized drugs. Instead, the Fifth Circuit merely upheld the "safe harbor" provision of section 503A, which offers a narrow exception for pharmacies engaged in the traditionally narrow compounding role (including, among other things, making individually tailored drugs in response to physician's prescriptions and not regularly replacing commercially available products). Section 503A draws a line between traditional compounding and drug manufacturing that is similar to the line the FDA has adopted for determining when to apply its "enforcement discretion" in the Ninth Circuit and other jurisdictions. Nothing in section 503A or the FDA's enforcement discretion policy protects the kind of large-scale drug manufacturing being carried out by the NECC and similar companies. Thus, the FDA had the authority to regulate pharmacies who engage in large-scale drug manufacturing, regardless of whether that manufacturing occurs in the Fifth Circuit or elsewhere in the United States.

  With appropriate use of this authority, the FDA could have more promptly taken action to shut down the NECC and prevented much of the subsequent fungal meningitis disaster that occurred.

  Nevertheless, Public Citizen supports enactment of carefully crafted federal legislation that would: (1) verify the FDA's authority over compounding pharmacy activities and (2) enhance that authority by also establishing minimum safety and quality standards for all drugs prepared by compounding pharmacies engaged in the traditional compounding role (specifically, preparing individually tailored drugs for patients having unique medical needs that cannot be met by a commercially available, standard drug manufactured by a pharmaceutical company).

It would be reasonable to use the provision of section 503A as enacted under FDAMA, excluding the advertising-related provision found to be unconstitutional, as a starting point for this new legislation. Public Citizen recommends the following regarding such legislation:

(1) The legislation should include a clearly defined, strictly limited safe harbor for the traditionally narrow role filled by local compounding pharmacies involving the preparation of a customized drug for a single identified patient. Such a provision would exempt these activities from the requirements for FDA approval of a new drug prior to marketing and good manufacturing practice (GMP). Once this safe harbor has been established, the FDA would no longer need to repeatedly use its enforcement discretion to avoid taking compliance actions against these pharmacies for violations of the FDCA, a practice on which the FDA has relied over the past several decades. This safe harbor should only encompass the compounding of drugs for single, identified patients with a prescription from a licensed health care provider and should exclude compounding copies of commercially available drugs.

Ideally, there should be no exceptions to the conditions that allow a compounding pharmacy to produce and dispense a drug within this safe harbor. However, if a critical need for exceptions is identified, any waivers of the conditions for the safe harbor should be very narrowly defined and should be time-limited (e.g., no more than one year) in order to avoid creating substantial loopholes that would allow wide-scale production of standardized versions of drugs under the guise of a compounding pharmacy. Any such waivers should be administered only by the FDA, to avoid variability in state regulations and the corresponding risk that citizens in one state will be threatened by drugs manufactured under weak regulations in another state.

(2) The legislation should require that any bulk substance used to produce a compounded drug be manufactured by an establishment registered under section 510 of the FDCA.

(3) The legislation should require that pharmacists or physicians compounding drugs comply with the standards of all applicable United States Pharmacopoeia chapters on pharmacy compounding.

(4) The legislation should prohibit compounding drug products: (a) whose compounding is reasonably likely to cause adverse effects on the safety or effectiveness of such products, or (b) that have been withdrawn or removed from the market because they have been found to be unsafe or ineffective.

(5) The legislation should authorize the FDA to issue a list of drugs that may not be compounded.

(6) The legislation should authorize FDA to establish an advisory committee to advise the Secretary on all issues related to compounded drugs.

- Should the current language in 503A be modified in any other ways?

Public Citizen's Response: In addition to our recommendations in the preceding response, Public Citizen recommends the following:

(1) The legislation should create an absolute firewall between compounding pharmacies that can take advantage of the safe harbor described in paragraph (1) of our response to the preceding question and any entity like the NECC that engages in scaled-up production and distribution of standardized versions of drugs and thus acts like, as should be regulated as, a drug manufacturer. This will prevent pharmacies from unfairly competing with drug manufacturers, who must comply with FDA new-drug approval and GMP requirements. Once unfair competition is removed, drug manufacturers will be better able to invest in meeting regulatory standards, the number of drug shortages will decrease, and more consumers will have access to drugs made under the highest-quality safety standards.

Public Citizen prefers that such a firewall be established by: (1) revising Section 510(g)(1) of the FDCA to exempt from registration requirements only those companies who engage *exclusively* in drug compounding that qualifies for the safe harbor,[7] and (2) excluding entities that are required to register under Section 510 from taking advantage of the "safe harbor" provision.

As an alternative, a firewall could be established by requiring entities engaged in "drug manufacturing" (defined by FDA regulation) to register under 510, and excluding registered entities from qualifying for safe harbor. However, Public Citizen does not prefer this option because it is more flexible and therefore subject to abuse by pharmacies wishing to scale up production while evading manufacturing regulations.

(2) The legislation should require pharmacists and physicians who compound drugs to report to the FDA: (a) any adverse event associated with the use of such drugs, and (b) any information concerning microbiological contamination; any significant chemical, physical, or other changes; or any deterioration of a compounded drug product that has been distributed by the pharmacist or

[7] This amendment is necessary because the current wording of Section 510 fails to draw a clear line between drug manufacturing and pharmacy compounding. Instead, it excludes from registration requirements all licensed pharmacies "which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drug devices for sale other than in the regular course of their business of dispensing drugs or devices at retail." FDCA section 510(g)(1) *codified as* 21 U.S.C. § 360(g)(1). Under the current wording, pharmacies may avoid registering as manufacturers by claiming to manufacture drugs only "in the regular course of their business."

physician that could cause serious injury or death. There should be mandatory deadlines for making such reports once the pharmacist or physician becomes aware of the adverse event or information.

(3) Legislation should require that the labels for all compounded drugs include the following warning:

> ***This drug has not been tested for safety and effectiveness and is not approved by the FDA. Serious adverse reactions to this drug should be reported to the pharmacy where it was received and to the FDA at [insert contact information].***

Furthermore, all patients receiving a compounded drug should be provided with this same warning in writing prior to the drug being dispensed or administered.

(4) The legislation should amend section 704(a)(2) of the FDCA to indicate that the exemption at subparagraph (A) does not apply to any compounding pharmacy that engages in scaled-up drug production and distribution (i.e., drug manufacturing).

(5) The legislation should require companies wishing to take advantage of the safe harbor provision to register with the FDA as compounding pharmacies. (This registration requirement would be distinct from the requirements for drug manufacturers under section 510.) The legislation should also require the FDA to make all registration applications publicly viewable in a national database.

(6) The legislation should clarify the FDA's existing authority to enter and inspect companies in order to ensure continued compliance with the requirements of the "safe harbor" provision. While the FDA currently has the authority to inspect compounding pharmacies, it has faced legal challenges in attempting to exercise that authority.[8] Regardless of the merit of such challenges, Congress could help avoid the expense of further litigation by clarifying the FDA's inspection authority in any new legislation replacing 503A.

FDA inspection records should also be promptly made available in a publicly accessible national database.

(7) The legislation should require states to report to the FDA any state enforcement actions taken against compounding pharmacies operating under the safe harbor provision. Those records should also be made available in a publicly accessible, national database.

(8) The legislation should authorize the FDA to promulgate regulations requiring pharmacies to regularly report information necessary to ensure compliance with

[8] *See* Med Ctr. Pharm. V Holder, 634 F.3d 830 (5th Cir 2011).

the safe harbor provisions. Such reports should be made available in a publicly accessible, national database.

- Should the anticipatory compounding language in (a)(2) be maintained or modified in any way?

  Public Citizen's Response: Such language is unnecessary and should be eliminated to prevent abuse. Any patient seeking to file multiple prescriptions based on any "history" of medication use can easily do so by requesting that their prescription include a specified number of refills. This is a standard practice that helps assist physicians in monitoring their patients' progress by requiring physician oversight at appropriate intervals. When a patient nears their limit on refills, their pharmacist should notify the patient to request a new prescription with additional refills to avoid any unnecessary delay. Section (a)(2) is therefore unnecessary and should be eliminated to stop pharmacies from evading compliance by claiming that drugs manufactured without a prescription were produced based on "history" for previous customers.

- Should the ban on compounding copies of commercially available drugs in (b)(1)(D) be maintained or modified?

  Public Citizen's Response: Such a ban should be maintained but modified to prevent abuse by removing the words "regularly or in inordinate amounts (as defined by the Secretary)."

- Should the 5% cap on interstate shipments in (b)(3) be maintained or modified? If the cap is retained, should the Secretary be authorized to develop a waiver process? If so, what should this process look like?

  Public Citizen's Response: Public Citizen supports limits on interstate shipments by compounding pharmacies taking advantage of the safe harbor provision in any new legislation replacing section 503A.

- Should we retain the MOU provision in 503A? Please discuss any challenges with that provision. Are there any other alternative measures that would increase communication and coordination between FDA and State Boards of Pharmacy?

  Public Citizen's Response: Public Citizen acknowledges that MOUs between the FDA and state pharmacy boards generally would be useful for establishing oversight responsibilities and communication channels with respect to compounding pharmacies engaged in traditional compounding activities under the safe harbor provision in any new legislation replacing section 503A. However, for those compounding pharmacies that engage in scaled-up drug production and distribution (i.e., drug manufacturing), primary oversight responsibility should remain with the FDA and should not be delegated to the states, even states operating under an MOU.

Good Compounding Practices:

- Should there be a federal requirement for compounding pharmacies to comply with USP standards for pharmaceutical compounding?
  Public Citizen's Response: Yes

- Are there other standards that would be more appropriate?

  Public Citizen's Response: Compliance with GMP standards may be more appropriate in some cases (such as sterile injectable drugs).

- Should any good compounding practices requirement apply to all compounded products, or only a subset (e.g. sterile compounding, compounding in particular types of facilities?)

  Public Citizen's Response: Such requirements should apply to all compounded products.

- How could federal good compounding standards be enforced?

  Public Citizen's Response: As described above, the legislation should authorize inspections and monitoring by the FDA if necessary to supplement any monitoring by state pharmacy boards conducted under state licensing laws or under regulations developed under an FDA/state MOU. State pharmacy boards should also be required to report to the FDA any enforcements actions taken by the state against a compounding pharmacy.

Scale of Compounding:

- Should any federal legislation distinguish between traditional compounding and large-scale compounding that more closely approximates manufacturing? If so, how should we define the two practices?

  Public Citizen's Response: Yes, federal legislation should distinguish traditional compounding from scaled-up compounding. As described above, Public Citizen recommends drawing a bright line (firewall) between compounding and manufacturing based on the requirements of the safe harbor provision. Companies should be allowed to engage in compounding or manufacturing, but not both.

- Can criteria like volume, percentage of sales that are compounded product, standardization of drug products, or interstate sales inform that definition? If so, how? We would welcome proposed definitions drawing lines between practices that should and should not be encompassed.

  Public Citizen's Response: As stated, Public Citizen recommends drawing a bright-line rule between compounding and manufacturing.

If such a bright line is rejected in favor of a more flexible standard, then some of the factors listed in this question may be useful in defining that standard. We do not have specific numbers for defining these parameters. The FDA should solicit comments on these issues during the rulemaking process that would follow enactment of any new legislation replacing section 503A.

Type of Compounding:

- Should any federal legislation differentiate between types of compounded products, for example as sterile or non-sterile, products used for particular applications, or by some other measure? What other measures might be appropriate? If divisions by product type are appropriate, should facilities producing different types of products be subject to different federal requirements?

  Public Citizen's Response: Federal regulations should impose stricter standards for sterile compounded drugs. For example, as previously noted, compliance with GMP standards may be more appropriate for sterile injectable drugs, whereas compliance with USP standards is adequate for nonsterile drug products.

Interstate Shipment:

- Do states take actions to ensure an out-of-state pharmacy complies with their state pharmacy laws? What are best practices for state oversight of non-resident pharmacies? Are there any mechanisms for purchasers in one state to evaluate a compounding facility out of state? If so, how frequently are those mechanisms used? If not, should there be?

  Public Citizen's Response: Public Citizen is unsure what actions states currently take to ensure that out-of-state pharmacies comply with their state pharmacy laws. Compounding pharmacies that engage in drug manufacturing and interstate commerce must be regulated by the FDA and not states. States are not well-positioned to safely regulate such activities.

- How many states have large scale compounding facilities that ship interstate?

  Public Citizen's Response: It is unclear to Public Citizen whether anyone has a definitive answer to this question. A statute requiring compounding pharmacies to register with the FDA and file regular reports to ensure compliance with federal requirements would be a good first step in helping to better track this information.

Ingredients in Compounded Products:

- What, if any, federal regulations should there around the bulk ingredients used in compounding? Should pharmacies be limited to using FDA-approved ingredients and/or ingredients from FDA-registered facilities in compounded products?

Public Citizen's Response: As previously noted, federal regulations should require that any bulk substance used to produce a compounded drug be manufactured by an establishment registered under section 510 of the FDCA.

- Should the use of marketed unapproved drugs be permitted in compounding?

  Public Citizen's Response: No

Registration or Listing:

- Should pharmacies be required to register or list with FDA? Should registration or listing be limited only to compounding pharmacies, compounding pharmacies that engage in sterile compounding, compounding pharmacies that sell their products across state lines, or some combination thereof?

  Public Citizen's Response: As previously noted, Public Citizen recommends that all compounding pharmacies be required to register with the FDA.

  Federal legislation should also more explicitly require that any compounding pharmacy that engages in scaled-up drug production and distribution (i.e., drug manufacturing) be required to register with the FDA as a drug manufacturer under section 510, as discussed above.

- If registration or listing is required, what fields of information should be included?

  Public Citizen's Response: The fields of information required to register compounding pharmacies should be the same as those required to register a drug manufacturer. In addition, the FDA should be authorized to promulgate regulations requiring regular reporting of information necessary to assure compliance with federal compounding requirements, as described above.

- Should firms subject to registration or listing pay a modest fee to cover FDA's costs of establishing the registration or listing program?

  Public Citizen's Response: Yes.

- Are there requirements associated with traditional registration or listing that would or would not be appropriate for entities engaged in compounding?

  Public Citizen's Response: As stated above, pharmacies registered with the FDA should be subject to inspection requirements, as are drug manufacturers registered under Section 510.

The Prescription:

- Should there be a federal requirement that compounded products be made only in response to a prescription? Or in anticipation of a prescription based on previous sales? If so, should there be a federal requirement that the prescription or notation ordering a compounded drug product explicitly call for the drug to be compounded?

  Public Citizen's Response: As previously noted, federal legislation should include a clearly defined, strictly limited safe harbor for the traditionally narrow role filled by local compounding pharmacies involving the preparation of a customized drug for a single identified patient with a prescription or notation order from a licensed health care provider. That prescription or notation should explicitly call for the drug to be compounded.

Office Stock:

- Should there be federal restrictions on compounding for office use? If so, what should the requirements or restrictions be?

  Public Citizen's Response: The requirements for all compounded drugs should be the same, regardless of whether the drugs are for office use, hospital use, or self-administration at a patient's home.

- Should the compounder be required to receive and/or reconcile prescriptions from the physician once the compounded product has been dispensed in the physician's office?

  Public Citizen's Response: In order for a compounded drug to be within the safe harbor discussed above as part of a revised section 503A, the drug should only be dispensed after the pharmacy receives a prescription for a specified individual patient who has unique medical needs that can only be met by compounding.

- Should the amount of product compounded for office stock be limited or capped in any way?

  Public Citizen's Response: Medical offices should not be permitted to stock drug products prepared by compounded pharmacies and instead should purchase drugs from drug manufacturers registered under section 510 unless individually tailored products are required for a particular patient.

- Should there be specific labeling requirements for compounded product for office use?

  Public Citizen's Response: Yes, as previously noted, federal legislation should require that the labels for all compounded drugs, including those for office use, include the following warning:

This drug has not been tested for safety and effectiveness and is not approved by the FDA. Serious adverse reactions to this drug should be reported to the pharmacy where it was received and to the FDA at [insert contact information].

Furthermore, all patients receiving a compounded drug should be provided with this same warning in writing prior to the drug being dispensed or administered.

- Should there be an allowance for compounding for research, teaching, or chemical analysis and not for sale or dispensing?

  Public Citizen's Response: For compounded drugs used in human subjects research, an investigational new drug application should be approved by the FDA prior to any such use of the drug. It may be reasonable to allow production of compounded drugs for purposes of animal or in vitro research, teaching, or chemical analysis under less restriction than those applicable to compounded drugs used in clinical care.

Standardized Drug Products:

- When, if ever, is it appropriate for a pharmacy to compound standardized drugs products (as opposed to a customized drug product based on individual's unique needs)?

  Public Citizen's Response: Compounding of standardized drug products, as opposed to a customized drug product addressing an individual's unique needs, by definition no longer involves compounding and instead crosses the line into drug manufacturing that should be strictly regulated by the FDA.

- Does it matter if the drugs at issue are not copies of commercially available drugs?

  Public Citizen's Response: No.

- How do the answers to these questions impact how office stock should be regulated?

  Public Citizen's Response: As previously noted, medical offices should not be permitted to stock drug products prepared by compounded pharmacies.

- How do you define standardized drug products?

  Public Citizen's Response: Standardized drug products involve preparation and distribution of multiple units of the same drug product formulation, not in response to a valid prescription for an individual patient.

Inspection Authority:

- Should FDA's authority to inspect compounding pharmacies and/or to access records of pharmacies be broadened? When, if ever, should there be a clear expectation that FDA (as

opposed to state authorities) will inspect compounding pharmacies? Should any enhanced FDA inspection authority be limited to particular types of compounding pharmacies?

Public Citizen's Response: As previously stated, the FDA already has authority to inspect compounding pharmacies, but that authority could be clarified to reduce enforcement costs.

- In your experience, has FDA had difficulty working with states to access records or to perform joint inspections?

Public Citizen's Response: We have no direct experience regarding whether the FDA has had difficulty working with states to access records or perform joint inspections. Media reports regarding the NECC in the wake of the fungal meningitis outbreak suggest that any such interactions and communications between the FDA and states in overseeing compounding pharmacies have been grossly inadequate. This clearly is an issue that the HELP Committee should evaluate as part of its investigation into the FDA's failures that contributed to the meningitis outbreak.

Compounded Product Labeling:

- Should there be a required disclaimer on the labeling of compounded drugs that notifies practitioners and consumers that the product at issue is compounded? If so, what should this disclaimer look like?

Public Citizen's Response: Yes, as previously noted, federal legislation should require that the labels for all compounded drugs include the following warning:

> ***This drug has not been tested for safety and effectiveness and is not approved by the FDA. Serious adverse reactions to this drug should be reported to the pharmacy where it was received and to the FDA at [insert contact information].***

Furthermore, all patients receiving a compounded drug should be provided with this same warning in writing prior to the drug being dispensed or administered.

Adverse Event Reporting:

- What, if any, adverse event reporting requirements currently apply with respect to compounded drug products?

Public Citizen's Response: It is our understanding that there is no federal requirement regarding reporting of adverse events associated with the use of compounded drugs.

- Should compounding pharmacies be required to report all or a subset of adverse events to FDA? Should such a requirement be limited to only certain pharmacies that engage in compounding?

Public Citizen's Response: Yes, as previously noted, federal legislation should require pharmacists and physicians who compound drugs to report to the FDA: (a) any adverse events associated with the use of such drugs, and (b) any information concerning microbiological contamination; any significant chemical, physical, or other changes; or any deterioration of a compounded drug product that has been distributed by the pharmacist or physician that could cause serious injury or death.

Federal and State Coordination and Communication:

- How well do federal and state officials coordinate existing authorities?

  Public Citizen's Response: We have limited knowledge regarding how well federal and state officials coordinate their existing regulatory authorities with respect to compounding failures. Media reports regarding the NECC in the wake of the fungal meningitis outbreak suggest that any such coordination was grossly inadequate. This clearly is an issue that the HELP Committee should evaluate as part of its investigation into the FDA's failures that contributed to the meningitis outbreak.

- Are adequate mechanisms in place to ensure appropriate communication between state and federal regulators with respect to oversight of compounding pharmacies? If not, how could such communication be improved?

  Public Citizen's Response: Again, we have limited knowledge regarding the mechanisms of ensuring appropriate communications between federal and state officials with respect to oversight of compounding failures. Media reports regarding the NECC in the wake of the fungal meningitis outbreak suggest that any such communications were grossly inadequate. This clearly is an issue that the HELP Committee should evaluate as part of its investigation into the FDA's failures that contributed to the meningitis outbreak.

- Should there be a specific federal requirement to coordinate enforcement and regulatory activities with respect to compounding pharmacy with state officials?

  Public Citizen's Response: Yes, there should be a specific federal requirement for the FDA to coordinate enforcement and regulatory activities with respect to any compounding pharmacy that take advantage of the safe harbor described above. For those compounding pharmacies that engage in drug production that falls outside the safe harbor, the FDA should be the sole agency enforcing the requirements of the FDCA related to new drug approval and GMP standards.

PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Appendix: Excerpts from a Sample of FDA Documents Demonstrating the Agency's Consistent Assertion that the Agency has Legal Authority over Compounding Pharmacies, 2002-2012

Compliance Policy Guides Manual – Section 460.200 Pharmacy Compounding[1]

> FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.
>
> FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in **manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act** [emphasis added]. Such establishments and their activities are the focus of this guidance. Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of receiving a valid prescription for them. Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship. **Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers** [emphasis added]. …
>
> However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action. …
>
> **FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution. Charges may include, but need not be limited to, violations of 21 U.S.C. §§ 351(a)(2)(B), 352(a), 352(f)(1), 352(o), and 355(a) of the Act** [emphasis added].

[1] The Food and Drug Administration. CPG Sec. 460.200 pharmacy compounding. May 29, 2002. Available at http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm. Accessed October 22, 2012.

December 9, 2004, warning letter to Lincare, Inc., and Reliant Pharmacy Services, Clearwater, Florida[2]

> [T]he agency now utilizes its longstanding policy of exercising its **enforcement discretion** regarding certain types of pharmacy compounding [emphasis added]. This policy is articulated in Compliance Policy Guide (CPG), Section 460.200, issued on June 7, 2002. The CPG contains factors the agency considers in deciding whether to exercise its enforcement discretion. One factor the agency considers is whether a compounded product is a copy of a commercially available product and, if so, whether there is patient-specific documentation of a medical need for the compounded product.
>
> Based on our inspection, we have determined your operation is akin to that of a drug manufacturer. Relevant findings include the following:
>
> - Your firm's acetylcysteine products are the same strengths (10% and 20%) as those available commercially. The commercial products are available as 10 ml and 30 ml multidose vials, whereas your firm's products are available as 0.5 ml and 5 ml single dose vials. We do not view the availability of single-dose vials as meaningful distinction between your products and commercially available products.
>
> - The strengths and sizes of your firm's budesonide products are the same as the commercially available products. We acknowledge the commercially available products are suspensions and your firm's products are solutions, but we do not regard this as a meaningful distinction and your firm's records fail to document patient-specific medical need for the compounded solutions. There is also no documentation physicians were told of and/or approved the use of your compounded products in lieu of the commercially available, FDA-approved products. …
>
> **Your firm's operation violates the following Sections of the Act** [emphasis added]:
>
> Section 505
> Your firm's inhalation solutions are "drugs" and "new drugs" within the meaning of Sections 201(g) and (p), respectively, of the Act. Under Section 505 of the Act, **they may not be introduced or delivered for introduction into interstate commerce because they lack approved applications** [emphasis added].
>
> Section 502(o)
> Since your firm manufactures and dispenses drugs in a manner exceeding the bounds of traditional pharmacy compounding, it is not exempt from the registration and drug listing requirements under 21 CFR 207.10 and Section 510 of the Act. Thus, **your drug products are misbranded under Section 502(o) of the Act** because they are not listed or manufactured in a duly registered establishment [emphasis added].

[2] The Food and Drug Administration. Warning Letter to Lincare, Inc. and Reliant Pharmacy Services, Inc. December 9, 2004. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2004/ucm146702.htm. Accessed October 22, 2012.

> In addition to the above violations as a drug manufacturer, **you must comply with the Act's Current Good Manufacturing Practice requirements (Section 501(a)(2)(B) of the Act and 21 CFR 211)** [emphasis added].

December 4, 2006, warning letter to the New England Compounding Center, Framingham, Massachusetts.[3]

> FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); Prof'ls & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); In the Matter of Establishment Inspection of**:** Wedgewood Village Pharmacy, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), aff'd, Wedgewood Village Pharmacy v. United States, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). **FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval** [emphasis added]. …
>
> Through the **exercise of enforcement discretion**, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding [emphasis added]. Rather, **FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA** [emphasis added]. …
>
> Further, on December 16, 2004, trypan blue ophthalmic solution was approved by FDA and it is commercially available. **As stated in the CPG, FDA will not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products**, including this one [emphasis added].
>
> All products compounded by your firm containing trypan blue or [aminolevulinic acid] **are drugs within the meaning of section 201(g) of the FDCA** (21 U.S.C. § 321(g)) [emphasis added]. **These products are misbranded under section 502(f)(1) of the FDCA** (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use [emphasis added]. They are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA and **they lack approved applications filed pursuant to section 505 of the FDCA** (21 U.S.C. § 355) [emphasis added]. …

[3] The Food and Drug Administration. Warning letter to the New England Compounding Center. December 4, 2006. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076196.htm. Accessed October 22, 2012.

> The Extra Strength Triple Anesthetic Cream compounded by your firm **is a drug within the meaning of section 201(g) of the FDCA** (21 U.S.C. § 321(g)) [emphasis added]. **This product is misbranded under section 502(f)(1) of the FDCA** (21 U.S.C. § 352(f)(1)) in that its labeling fails to bear adequate directions for its use [emphasis added]. It is not exempt from this requirement under 21 CFR § 201.115, because it is a new drug within the meaning of section 201(p) of the FDCA that **lacks an approved application filed pursuant to section 505 of the FDCA** (21 U.S.C. § 355) [emphasis added]. …
>
> Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional material offers this drug to ophthalmologists. Avastin has no approved indications for use in the eye. As such, **your firm is distributing an unapproved new drug in violation of section 505 of the FDCA** [emphasis added]. Because the product **lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA** (21 U.S.C. § 352(f)(1)) [emphasis added]. Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited.
>
> **Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited** [emphasis added].

December 5, 2006, FDA news release entitled *FDA Warns Five Firms to Stop Compounding Topical Anesthetic Creams*[4]

> The Food and Drug Administration (FDA) is **warning five firms,** Triangle Compounding Pharmacy, University Pharmacy, Custom Scripts Pharmacy, Hal's Compounding Pharmacy, and New England Compounding Center, **to stop compounding and distributing standardized versions of topical anesthetic creams, which are marketed for general distribution rather than responding to the unique medical needs of individual patients** [emphasis added]. **Firms that do not resolve violations in FDA warning letters risk enforcement such as injunctions against continuing violations and seizure of illegal products** [emphasis added]. …
>
> FDA-approved topical anesthetic products are commercially available and properly labeled, and are regularly used in health-care settings. However, some pharmacies create their own standardized versions of these products, often including combinations of ingredients and ingredients at higher strengths than found in FDA-approved products, and often lacking appropriate warnings or directions for use.
>
> The five firms warned by FDA have stated that they produce their topical anesthetic creams as part of the practice of pharmacy compounding. Traditional pharmacy compounding typically involves pharmacies preparing drugs that are not commercially

[4] The Food and Drug Administration. FDA news release: FDA warns five firms to stop compounding topical anesthetic creams. December 5, 2006. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108793.htm. Accessed October 22, 2012.

available, such as a unique medicine for a patient who is allergic to an ingredient in a FDA-approved drug. This kind of compounding follows a physician's decision that his or her patient has a special medical need that cannot be met by FDA-approved drugs.

FDA normally permits such traditional pharmacy compounding and the agency's action is not targeting this practice. By contrast, **FDA is concerned that the five firms receiving warning letters are behaving like drug manufacturers, not traditional compounding pharmacies, because they produce standardized versions of topical anesthetic creams for general distribution** [emphasis added].

January 7, 2008, warning letter to Pharmacy Compounding Specialties, Dallas, Texas[5]

Under section 502(a) of the FDCA, a drug is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the FDCA [21 U.S.C. § 321(n)] provides that, in determining whether a drug's labeling or advertising "is misleading, there shall be taken into account... not only representations made or suggested... but also the extent to which the labeling or advertising... fails to reveal facts material in light of such representations...."

Your website advises that you compound hormone therapy drugs that are available for purchase and distribution. **These compounded hormone therapy drugs are misbranded within the meaning of section 502(a) of the FDCA for the following reasons** [emphasis added]:

1. Unsubstantiated Efficacy Claims…

Your firm's website contains claims concerning your firm's compounded hormone therapy drugs, including:
- "Protection against fibrocystic breast disease"
- "Protection against cardiovascular disease, the #1 killer of women"
- "Acts as a natural antidepressant and enhances sleep"
- "Maintains thyroid function and normalizes blood sugar levels"

FDA regards these claims as false and misleading. FDA is not aware of substantial evidence (consisting of adequate and well controlled clinical investigations) that supports these claims.

2. Unsubstantiated Superiority Claims

Your firm's website contains a statement suggesting the superiority of your firm's compounded hormone therapy drugs:

-"Progesterone-not to be confused with synthetic progestins cited in the published studies as putting women at risk of disease and the side effects of fluid retention, irritability and depression, natural progesterone has many positive benefits."

[5] The Food and Drug Administration. Warning letter to Pharmacy Compounding Specialties. January 7, 2008. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048445.htm. Accessed October 22, 2012 .

This statement represents and suggests that your firm's compounded hormone therapy drugs are superior to other hormone therapy products, including FDA-approved drugs. This claim—which is unsupported by substantial (consisting of adequate and well controlled clinical investigations)—is false and misleading.

3. Unsubstantiated "Bio-identical" Claims

Your website claims that your firm's compounded hormone therapy drugs are "bio-identical." This claim implies that your compounded hormone therapy drugs are natural, or identical to the hormones made by the body. FDA is unaware of substantial evidence (consisting of adequate and well controlled clinical investigations) to support the claimed "bio-identical" nature of your hormone therapy drugs.

As explained above, the claims made for your hormone therapy drugs are false and misleading in that they are not supported by substantial evidence. These claims cause your hormone therapy drugs to be misbranded under section 502(a) of the FDCA [emphasis added].

B. Unapproved New Drug Under Section 505 of the FDCA: Estriol

Because your products are intended to treat, mitigate, and prevent disease (a conclusion supported by the claims described above), **the estriol products compounded by your firm are drugs within the meaning of section 201(g) of the FDCA** [21 U.S.C. § 321(g)] [emphasis added]. Further, **as these products are not generally recognized by qualified experts as safe and effective for their labeled uses, they are new drugs, as defined by section 201(p) of the FDCA** [21 U.S.C.§ 321(p)] [emphasis added]. No FDA-approved applications pursuant to section 505 of the FDCA [21 U.S.C. § 355] are effective with respect to these drugs.
Accordingly, their introduction or delivery for introduction into interstate commerce violates section 505(a) of the Act [21 U.S.C. § 355(a)] [emphasis added].

The FDCA establishes agency jurisdiction over "new drugs," including compounded drugs. Compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts... as safe and effective" for their labeled uses. …

The drugs that pharmacists compound are not FDA-approved and thus lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. *See Thompson v. Westem States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced drug, or diluted dosages for children.

FDA's current enforcement policy with respect to the compounding of human drugs is articulated in Compliance Policy Guide section 460.200 ["Pharmacy Compounding"],

issued by FDA on May 29, 2002 (*see Notice of Availability*, 67 Fed. Reg. 39,409 (June 7, 2002)). The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors include whether a firm is "[c]ompounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312."

November 12, 2008, warning letter to Steven's Pharmacy, Costa Mesa, California[6]

Your firm purports to be a compounding pharmacy, but our investigation found that **your operation exceeds the practices associated with traditional extemporaneous compounding and is more akin to that of a drug manufacturer** [emphasis added]. Your firm manufactures large volumes of drugs including, but not limited to, **[(b)(4)]** standardized topical anesthetic drugs ("Profound Gel," and "Profound Gel Light"), **[(b)(4)]** products in anticipation of receiving prescriptions. …

The production of these volumes of standardized prescription drug products is inconsistent with traditional extemporaneous compounding, which involves compounding a medication based on a specific medical need of an individually-identified patient. For commonly ordered compounded prescription drugs, your firm produces drugs in anticipation of receiving prescriptions. Such anticipatory inventory of topical anesthetic drugs was noted during the recent FDA inspection of your firm. …
In addition to producing drug products in anticipation of receiving prescriptions, your firm produces large volumes of compounded products, including copies of FDA-approved commercially available products. Examples include **[(b)(4)]** and **[(b)(4)]**. Other products compounded by your firm are essentially copies of FDA-approved commercially available products, including alternate oral dosage forms, such as **[(b)(4)]** These essential copies appear to be produced without a documented patient-specific medical need, as determined by a licensed healthcare provider, for these versions of otherwise commercially available drugs.

During the inspection, you stated that approximately **[(b)(4)]** of all finished drug products are distributed outside of California. **Your firm is engaged in the commercial-level distribution of standardized drug products, as you provide preprinted order forms and promotional material to practitioners and obtain orders from dentists that contain a list of drugs to be compounded by your firm**, including for your topical anesthetic prescription drug products [emphasis added]. Moreover, the use of the terms "Profound Gel" and "Profound Gel Light" implies the standardization of a compounded drug product rather than extemporaneous compounding for individually-identified patients. **This practice is outside the traditional scope of pharmacy compounding and more akin to that of a drug manufacturer** [emphasis added]. …

[6] The Food and Drug Administration. Warning letter to Steven's Pharmacy. November 12, 2008. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048074.htm. Accessed October 22, 2012.

C. Violations of the FDCA

Unapproved New Drug Products

The aforementioned products made by your firm **are drugs within the meaning of Section 201(g) of the FDCA** [21 USC § 321(g)] [emphasis added]. **These products are new drugs as defined by Section 201(p) of the FDCA** [21 USC § 321(p)], because they are not generally recognized by qualified experts as safe and effective for their labeled uses [emphasis added]. No approved application pursuant to Section 505 of the FDCA [21 USC § 355] is in effect for these products. Accordingly**, their introduction or delivery for introduction into interstate commerce violates Sections 505(a) and 301(d) of the FDCA** [21 USC §§ 355(a) and 331(d)] [emphasis added].

Misbranded Drug Products

Your firm's drug products are misbranded under Section 502(1)(1) of the FDCA [21 USC § 352(f)(1)] because their labeling fails to bear adequate directions for use [emphasis added] and they are not exempt from this requirement under Title 21, **Code of Federal Regulations** [emphasis in original], Part 201, Section 115 (21 CFR§ 201.115).

Your firm's drug products are also misbranded under Section 502(o) of the FDCA [21 USC § 352(o)] **because they are manufactured in an establishment not duly registered under Section 510 of the FDCA** [21 USC § 360], and the articles have not been listed as required by Section 510(j) of the FDCA [21 USC § 360(j)] [emphasis added]. Your facility is not exempt from registration and drug listing requirements under 21 CFR § 207.10 or Section 510(g) of the FDCA [21 USC § 360(g)]. **Your firm's topical anesthetic drug products, including Profound Gel and Profound Gel Light, are misbranded under Section 502(a) of the FDCA [21 U.S.C. § 352(a)], as further defined in Section 201(n), 21 U.S.C. § 321(n), because their labels fail to reveal adequate information to support the safe use of the products, contain limited dosing information, and contain no clear indication and intended route of administration, facts material with respect to adverse health consequences that may result from the use of the articles by individuals with underlying medical conditions or those otherwise at risk for adverse drug side effects** [emphasis added].

D. Conclusion…

You should take prompt action to correct the violations cited in this letter. **Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction** [emphasis added].

September 28, 2009, warning letter to Hopewell Pharmacy and Compounding Center, Hopewell, New Jersey[7]

> [T]his Warning Letter concerns Hopewell's compounding of Sodium Tetradecyl Sulfate (STS) Injection, 2%, 4% and 5%. **The STS Injection, 2%, 4% and 5% strengths made by Hopewell are drugs within the meaning of section 201 (g) of the Federal Food, Drug, and Cosmetic Act (FDCA)** [21 U.S.C. § 321 (g)] [emphasis added]. As discussed below, **these drugs and your production and distribution of these drugs violate the FDCA** [emphasis added].
>
> Factual Background
>
> On June 4, 2008, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, located at West Broad Street, Hopewell, NJ. During the inspection, our investigator collected samples of Sodium Tetradecyl Sulfate (STS) finished product and active pharmaceutical ingredient. The Hopewell, NJ facility is licensed by the State of New Jersey Board of Pharmacy as a retail community pharmacy. **The June 2008 inspection was a follow-up to assess whether commitments made during the October 2006 FDA inspection, regarding the discontinuation of the compounding of STS Injection, 1% and 3%, were upheld** [emphasis added]. This inspection found that your firm currently compounds STS Injection, 2%, 4% and 5% only. On June 4, 2008, FDA collected samples, consisting of 6 finished vials of STS Injection, 4%; 6 finished vials of STS Injection, 5%; STS aqueous stock solution, 27%; and the powder STS active pharmaceutical ingredient. These samples were subsequently analyzed by FDA and determined to be adulterated due to the presence of a contaminant, diethylene glycol monoethyl ether (DEGMEE), in the STS finished products and the STS aqueous stock solution.
>
> Violations of the FDCA
>
> *Adulterated Drug Product*
>
> Analysis of the 6 finished vials of STS Injection, 4%; the 6 finished vials of STS Injection, 5%; and the STS aqueous stock solution, 27% indicates the presence of the DEGMEE contaminant in the aqueous stock solution and finished product samples. **Hopewell's STS Injection, 4% and 5% are adulterated under section 501(c) and (d)(1) of the FDCA** [21 U.S.C. § 351(c) and (d)(1)] [emphasis added]. **These drug products are adulterated within the meaning of section 501(c) [21 U.S.C. § 351(c)] in that they are drugs that are not recognized in an official compendium and their strengths differ from, or their quality or purity fall below, that which they purport or are represented to possess** [emphasis added]. Further, DEGMEE has not been studied for use in injectable drugs and there are no approved drugs for injection that contain this material.

[7] The Food and Drug Administration. Warning letter to the Hopewell Pharmacy and Compounding Center. September 28, 2009. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm188449.htm. Accessed October 22, 2012.

> Accordingly, there is no assurance of the safety of an injectable drug product containing DEGMEE. These drug products are also adulterated within the meaning of section 501(d)(1) of the FDCA [21 U.S.C. § 351(d)(1)] in that they are drugs and contain a substance, diethylene glycol monoethyl ether (DEGMEE), mixed therewith so as to reduce their quality or strength.
>
> Conclusion …
>
> You should take prompt action to correct the violations cited in this letter. **Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction** [emphasis added].

April 9, 2010, warning letter to J & F International Inc., dba Alexandria Medical Arts Pharmacy & Compounding Laboratory, Alexandria, Virginia[8]

> **The FDCA establishes agency jurisdiction over "new drugs," including compounded drugs** [emphasis added]. Compounded drugs fit within the FDCA's definition of "new drug": "[a]ny drug (except a new animal drug ...) [that] is not generally recognized ... as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321 (p)(1). See also Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"). **There is substantial judicial authority supporting FDA's position that compounded drugs are not exempt from the new drug definition** [emphasis added]. See Medical Ctr. Pharm. v. Mukasey, 536 F.3d 383 (5th Cir. 2008) ("compounded drugs are not exempt from the FDCA's 'new drug' definition, § 321(p), nor are they uniformly exempt from the FDCA's 'new drug' requirements, §§ 351(a)(2)(B), 352(f)(1), 355"); Prof'ls & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug ... provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); In the Matter of Establishment Inspection of Wedgewood Village Pharm., 270 F. Supp. 2d 525,543-44 (D.N.J. 2003) ("The FDCA contains provisions with explicit exemptions [from] the new drug ... provisions. Neither pharmacies nor compounded drugs are expressly exempted."), aff'd, Wedgewood Village Pharm. v. United States, 421 F.3d 263, 269 (3d Cir. 2005). **The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. Because compounded drugs are "new drugs" under the FDCA that are unapproved, the statute generally prohibits their introduction into interstate commerce** [emphasis added]. …
>
> In May of 2002, FDA issued a revised compliance policy guide (CPG) on pharmacy compounding, CPG Sec. 460.200 ["Pharmacy Compounding"], which explained how the Agency would address pharmacy compounding following the Supreme Court's decision. The CPG sets forth a non-exhaustive list of factors that FDA considers in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raise the kind of concerns ordinarily associated with drug manufacturing. …

[8] The Food and Drug Administration. Warning letter to J & F International Inc., dba Alexandria Medical Arts Pharmacy & Compounding Laboratory. April 9, 2010. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm208772.htm. Accessed October 22, 2012.

B. Factual Background

The April 2009 FDA inspection of your facility revealed, in a Monthly Audit Log dated from 11/01/08-04/06/09, that your firm compounded domperidone products for human patients on numerous occasions. FDA is concerned with the public health risks associated with the compounding of domperidone for human use. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from marketing in several countries. Among other uses, FDA has become aware of the use of domperidone by lactating women to increase breast milk production because of its effect on prolactin levels. While domperidone is approved in several other countries for the treatment of gastric stasis and gastroparesis, domperidone is not approved in any country for enhancing breast milk production in lactating women. In several countries where the oral form of domperidone continues to be marketed, labels for the product note that domperidone is excreted in the breast milk of lactating women and recommend that women taking domperidone avoid breast-feeding. Because of this, FDA recommends that breastfeeding women not use domperidone to increase milk production.

Compounding drugs using domperidone is inappropriate under both the CPG and section 503A of the FDCA (21 U.S.C § 353a) [emphasis added]. Under the CPG on human drug compounding, FDA considers whether a firm compounds finished drugs from bulk active ingredients that are not components of FDA approved drugs, without an FDA sanctioned investigational new drug application (IND). **Domperidone is not a component of an FDA approved drug, and FDA would not exercise its enforcement discretion for compounded human drugs containing domperidone** [emphasis added]. Further, under section 503A (b)(1)(A)(i) of the FDCA (21 U.S.C. § 353a(b)(1)(A)(i)), compounded drugs containing domepridone would not be eligible for the exemptions provided by section 503A of the FDCA (21 U.S.C § 353a) because domperidone is not the subject of an applicable USP or NF monograph, nor is it a component of an FDA-approved drug.

FDA understands that some patients may need domperidone to treat certain gastrointestinal disorders. Physicians who would like to prescribe domperidone for their patients may seek to open an IND through the established procedures. Information regarding obtaining an IND for Domperidone can be found at http://www.fda.gov/Drugs/DrugSafety/lnformationbyDrugClass/ucm073070.htm. It should be noted that the IND is obtained by the prescribing physician and not the pharmacy.

C. Violations of the FDCA

Misbranded and Unapproved New Drugs

The domperidone products compounded by your firm are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)] [emphasis added**]. They are also new drugs under section 201(p) [21 U.S.C. § 321(p)] of the FDCA because they are not generally recognized by qualified experts as safe and effective for its labeled uses** [emphasis added]. **These products may not be introduced or delivered into interstate**

> **commerce under section 505(a) of the FDCA [21 U.S.C. § 355(a)] because no approval of an application filed pursuant to section 505 of the FDCA [21 U.S.C. § 355] is in effect for these products** [emphasis added]. **Their introduction or delivery for introduction into interstate commerce violates section 301(d) of the FDCA** [21 U.S.C. § 331(d)] [emphasis added].
>
> **These products are also misbranded under 502(f)(1) of the Act in that their labeling fails to bear adequate direction for their use** [emphasis added]. Further, these products are not exempt from this requirement under 21 CFR § 201.115, because they are new drugs within the meaning of section 201(p) of the Act and they lack approved applications filed pursuant to section 505 of the Act. Section 301(a) of the FDCA [21 U.S.C. § 331 (a)] prohibits the introduction or delivery for introduction into interstate commerce of any misbranded drug, and section 301(k) of the FDCA [21 U.S.C. § 331(k)] prohibits any act with respect to a drug if the act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.
>
> D. Conclusion …
>
> You should take prompt action to correct the violations cited in this letter. **Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction** [emphasis added].

June 29, 2012, letter to Wedgewood Pharmacy, Swedesboro, New Jersey[9]

> This letter concerns the information that appears on your website regarding Wedgewood Pharmacy's compounding of 17-hydroxyprogesterone caproate (HC). HC is the active ingredient in Makena, which, as you know, the Food and Drug Administration (FDA) approved in February 2011 for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth.
>
> Your website includes a press release Wedgewood Pharmacy issued on March 30, 2011, which interprets a statement issued by FDA the same day. In the press release, titled "With FDA green light, Wedgewood Pharmacy continues to compound 17P (hydroxyprogesterone caproate)", Wedgewood Pharmacy acknowledged that "Under normal circumstances, compounding pharmacies must stop making a prescription drug when the same drug is manufactured as a commercial product." However, Wedgewood Pharmacy interpreted FDA's March 30, 2011, statement on Makena as "allow[ing] compounding pharmacies to continue" compounding hydroxyprogesterone caproate, and stated that it would "continue to prepare and dispense 1 ml, 5 ml and 10 ml multi-dose vials of 17P (Hydroxyprogesterone Caproate)." Wedgewood Pharmacy's press statement also explained that "for patients with certain sensitivities, for whom the use of Wedgewood Pharmacy's regular formulation of 17P is contraindicated, the company also will provide a preservative-free 17-alpha hydroxyprogesterone caproate, 250 mg/ml, in single-dose vials." In addition, your website includes a statement titled "FDA's Review of Compounded 17P Finds No Safety or Purity Issues for Enforcement Policy Change,"

[9] The Food and Drug Administration. Letter to Wedgewood Pharmacy. June 29, 2012. Available at http://www.fda.gov/downloads/NewsEvents/Newsroom/PressAnnouncements/UCM314387.pdf. Accessed October 22, 2012.

which states that "the FDA found no reason to change its enforcement policies regarding compounded Hydroxyprogesterone Caproate."

We are writing to ensure that Wedgewood Pharmacy is not operating under the misimpression that there is a "green light" to compound large volumes of copies of Makena. On June 15, 2012, FDA updated the March 30, 2011, statement on compounded versions of hydroxyprogesterone caproate. That statement explained:

> Compounding large volumes of drugs that are copies of FDA-approved drugs circumvents important public health requirements, including the Federal Food, Drug, and Cosmetic Act's drug approval provisions. Consumers and health professionals rely on the Act's evidence-based drug approval process to ensure that drugs are safe and effective. **For that reason, one factor that the agency considers in determining whether a drug may be compounded is whether the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product** [emphasis added].

The statement also emphasized that FDA is "**applying its normal enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate," and that the "compounding of any drug, including hydroxyprogesterone caproate, should not exceed the scope of traditional pharmacy compounding** [emphasis added]." A complete copy of the statement is available on FDA's website at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm.

As we explained in our October 31, 2006, Warning Letter to you, "[t]raditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children." The information on your website indicates that you compound copies of the commercially available product as well as a preservative-free formulation for patients unable to tolerate the product that contains the preservative. **You should be aware that FDA does not view compounding large volumes of drugs that are copies of FDA-approved drugs as traditional pharmacy compounding** [emphasis added].

The compounding of copies of commercially available drugs is addressed in both section 503A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 353a) and the Agency's compliance policy guide (CPG) on pharmacy compounding (CPG Sec. 460.200) [emphasis added]. For a drug to satisfy the conditions in section 503A, a pharmacist may "not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product." 21 U.S.C. § 353a(b)(1)(D). Similarly, the CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. One of the factors listed in the CPG is "Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly

different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient." CPG Sec. 460.200 at 4-5.

As stated above, **FDA does not consider compounding large volumes of copies, or what are essentially copies, of any approved commercially available drug to fall within the scope of traditional pharmacy practice. A pharmacy that engages in such compounding may be subject to enforcement action** [emphasis added].