



American Pharmacists Association[®]
Improving medication use. Advancing patient care.

January 18, 2013

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MT 20852

[Submitted electronically to: www.regulations.gov]

RE: Docket No. FDA-2012-N-1154. Framework for Pharmacy Compounding: State and Federal Roles

Dear Sir/Madam:

The American Pharmacists Association (APhA) appreciates the opportunity to provide comments to the Food and Drug Administration (FDA) on the regulatory framework for pharmacy compounding and the role for state and federal oversight, as discussed at FDA's intergovernmental meeting on December 19, 2012 (77 FR 71009). APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings and the uniformed services.

We support FDA's efforts to gather information from stakeholders as it continues to work with Congress and state boards of pharmacy to consider new regulatory authorities over non-traditional compounding pharmacies and to better regulate and define manufacturing. We believe that FDA does have a role to play when compounding practices start to look like manufacturing practices. We agree that FDA, states, Congress and stakeholders need to better define compounding and manufacturing and better delineate when the line is crossed and FDA involvement is needed to protect the public. APhA appreciates that FDA has consistently stated its support for traditional pharmacy compounding practices. We value open two-way communications with the Agency as compounding discussions continue.

APhA is committed to efforts enhancing patient safety while maintaining patient access to pharmacy compounding services. Our comments below build from: the December 2012 intergovernmental meeting; our discussions with FDA at the December 2012 pharmacy stakeholders listening session; our comments to the U.S. Senate Health, Education, Labor and Pension (HELP) Committee in November 2012; meetings with House Energy and Commerce

staff and our ongoing dialogue with Congressional and Agency staff, the pharmacy community, and other stakeholders.

We appreciate that FDA is considering a risk-based framework which would create two categories of compounding, including “traditional” and “non-traditional.” As proposed, traditional compounding would remain under the jurisdiction of the state. As discussed by FDA in testimony at the November 2012 Congressional hearings and December 2012 stakeholder meetings, traditional compounding would “include the combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need.”

In addition, FDA proposed non-traditional compounding as being subject to federal standard that, “would include certain types of compounding for which there is a medical need, but that pose higher risks based on one or more (of the) factors.” Such factors include “the amount of product being made or whether the drug is being dispensed to someone other than the ultimate user when it leaves the facility where it was produced.”

APhA believes that a tiered regulatory approach of traditional and non-traditional compounding has its merits, generally supports the concept, and is very interested in continuing dialogue with FDA, Congress, States and other stakeholders to explore potential solutions. As the concept evolves, we do recommend considering the following areas in which further clarifications and additions would be helpful regarding the regulation of the proposed traditional and non-traditional compounding categories.

- **Compounding Standards:** APhA supports efforts to ensure proper resources and funding for state boards of pharmacy for compounding regulatory activity. We recommend consideration that all states should require licensed pharmacies that compound to follow USP 795 non-sterile compounding and USP 797 sterile compounding standards depending on the types of compounding being performed in any practice setting. As differentiation between traditional and non-traditional compounding practices becomes more defined, and as oversight of such practice evolves, FDA and state boards of pharmacy should be provided the resources to train and deploy qualified inspectors to enforce appropriate regulations and should work with voluntary groups like the Pharmacy Compounding Accreditation Board (PCAB) to leverage existing resources by coordinating, and not duplicating efforts. With appropriate recognition, PCAB could play a role in significantly broadening adoption of high quality standards for compounding.
- **Sterile Compounding Licensure:** APhA supports consideration of enhanced standards and state licensure for sterile compounding to ensure consistent standards across all states and providers in all various practice settings. We encourage states to consider requiring a separate license and inspection by appropriately trained, knowledgeable and compounding experienced healthcare professionals for sterile compounding conducted in all pharmacy, medical and physician office, clinic and ambulatory, institutional, nuclear, and veterinary practice settings. Although the broad public health implications are great when large scale production of sterile products leads to broad distribution, it is still true that compounding a single dose of a drug for injection in a highly contaminated environment may be unsafe for the one patient who

receives it. It may be prudent for compounding pharmacies to limit production of sterile products. However, limiting the volume of doses of topical preparations may have little impact on safety. Therefore, we believe that a risk-based framework lends itself to consideration of sterile versus non-sterile compounding practices in conjunction with quantity of compounding. The quantity compounded and the distribution mechanism that might cross the line from State Board of Pharmacy inspection and oversight into manufacturing and FDA oversight needs to be clearly defined to both protect the public and to avoid confusion for pharmacy entities.

We also recommend that state boards of pharmacy specifically list what the board is responsible for regulating and what the board does not regulate – generally meaning such activities trigger FDA oversight. Such descriptions by state boards could help communicate the different regulatory oversight of traditional compounding, non-traditional compounding, and manufacturing, in addition to the role of interstate commerce.

- **Manufacturer versus Compounder:** APhA agrees with ongoing dialogue that the definition of compounding versus manufacturing needs to be clearly defined. These definitions are key for addressing confusion in the current market place, enhancing patient safety, and in improving regulatory oversight. If a compounding pharmacy in the non-traditional category begins to act like a manufacturer then they should be treated and regulated as a manufacturer. We support efforts to better determine when the line is crossed into manufacturing and ensuring FDA has the authority to step in to enforce current law when it is appropriate. If a compounding pharmacy becomes a manufacturer, APhA supports them being regulated and treated by FDA as a manufacturer. They should register and submit appropriate drug approval applications, and be subject to Good Manufacturing Practices. Furthermore, there must be consistency across state lines for criteria used to distinguish compounding from manufacturing. Federal legislation would help ensure that each state implements consistent requirements. Similarly, if FDA gains authority to regulate non-traditional compounding, transparency is needed to avoid confusion as to when states have authority or when FDA must regulate.
- **Amount/quantity:** Under the non-traditional compounding category, a clear definition is needed when referencing the amount of a product being made – or quantity of compounded product. If there is not a specifically stated volume or quantity level then smaller traditional compounding pharmacies may be affected and therefore regulated by the FDA. This could in turn affect patient access to these medications. Pharmacists who compound according to recognized professional standards and guidelines and state regulations help patients meet therapy goals and improve patient health and care outcomes. If these same pharmacists and pharmacies fall into the non-traditional category they might cease their important and safe compounding services if new additional requirements are too burdensome. For example, this could result in cancer patients having to look elsewhere for their medications when they have challenges with the ability to swallow or take medications in currently available forms. Oral and even sterile intravenous medications are frequently compounded into other dosage forms to meet that particular patient's needs. And, often pharmacies in the proximity of clinics and other facilities that serve these patients will produce various quantities based on history and short-term anticipated need.

We are also concerned that severe restrictions on quantities might impact a pharmacy's ability to compound products in anticipation of known prescription orders and refills and thus could eliminate system efficiencies. The ability for pharmacies to compound in anticipation of known prescription orders is a generally recognized standard of practice that needs to be maintained pursuant to appropriate compliance with existing regulations. If standards are met, these efficiencies should lower cost without affecting quality.

- **Compliance Policy Guide:** We encourage FDA to revise and to utilize the existing Compliance Policy Guide (CPG), Section 460. 200 Pharmacy Compounding as a tool to help ensure standards are referenced, and that appropriate guidance is given on use of definitions and regulatory oversight. For example, the CPG could be used to further emphasize that compounding of commercially available products (i.e. making copies of approved products) is not appropriate and could trigger FDA oversight. We have concerns when practices may be compounding such products by replacing a filler or preservative with no documented or apparent clinical reason for individual patient needs. We also recommend FDA use the CPG or other means to clarify when compounding based on a drug shortage is appropriate and allowed. Further, we recommend including discussion that it is inappropriate for a site to suggest compounding of a product due to perceived drug shortage issues when, due to the nature of a product, there may be short/small delays in stock while supplies are generally reliable.
- **Education and Training Resources:** While state boards of pharmacy have existing authority to regulate compounding, many states have cut (or not adequately expanded) budgets and thus may have inadequate resources to provide inspector training or properly conduct inspections and perform other compounding oversight activities. In order for states to appropriately regulate compounding, we advocate that boards of pharmacy must have adequate resources and must have a board composition with broad expertise (including sterile compounding). In addition, we strongly believe that pharmacists with experience performing sterile and complex compounding should be utilized in inspecting all practice sites performing higher level of compounding activities. We also support greater standardized training for state pharmacy board inspectors related to standards for compounding, identifying potential conflicts of interest, and better guidance/training on differentiating between traditional compounding practices versus activities that suggest manufacturing. Such standardized education and training would be beneficial for FDA inspectors as well.
- **Communication:** If a tiered system and risk-based framework evolves that differentiates compounding licensure and/or regulatory oversight versus manufacturing, there needs to be better communication between and among the state boards and FDA. If a Federal standard for non-traditional compounding was to be promulgated, we expect that FDA would be responsible for overseeing and enforcing such oversight. Such a change would require increased communication and coordination to improved transparency/awareness of regulatory activity and authority and ultimately benefit patient safety. We recognize that FDA and many state boards have resource challenges that impact inspection capacities and may benefit from having an option for a Memorandum of Understanding (MOU) as stated in 503A. Such an arrangement is analogous to the Nuclear Regulatory Commission (NRC) contracting with state agencies for regulation of radioactive material ("Agreement States"), similarly, FDA could contract with interested states to oversee and regulate such non-traditional

compounding. Additionally, we recommend FDA providing education and training for state boards acting in such capacity.

- **Accreditation:** Recognizing that community pharmacies are regulated by state boards and have a license that covers compounding practice, we believe that the public would benefit from greater practice site adoption of PCAB standards. PCAB maintains and updates standards that reflect contemporary best compounding practices. PCAB also provides compounding practices an opportunity to compare their practices against national standards and to achieve accreditation that provides consumers an indicator of quality practice. These standards have been in the market for several years and are regularly updated. To date, 168 compounding pharmacies have met PCAB standards for accreditation. APhA, as one of the founding members of PCAB, believes greater promotion of accreditation standards is an important consideration as dialogue continues. In addition, PCAB is in final stages of revising processes to limit the scope of eligibility criteria of PCAB accreditation that may be of assistance as state versus FDA oversight of compounding practices is reviewed. We recommend serious consideration of this process when implemented.

Finally, attached is an extensive comment letter APhA submitted to the Senate HELP Committee in November 2012 in response to Committee questions as they prepared for Congressional compounding discussions. We encourage FDA to review the document as we believe it is a helpful resource for ongoing dialogue between FDA, Congress, state boards of pharmacy and other stakeholders. Again, APhA offers our support and engagement with FDA as we work to ensure patient safety while maintaining access to compounded products.

Thank you for the opportunity to provide comments on this important issue. If you have any questions or require additional information, please contact Marcie Bough, PharmD, Senior Director of Government Affairs, at mbough@aphanet.org or by phone at (202) 429-7538.

Sincerely,



Thomas E. Menighan, BSPHarm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO

Enclosure

cc: Michael Spira, Senior Lobbyist, Government Affairs
Marcie Bough, PharmD, Senior Director, Government Affairs



American Pharmacists Association[®]
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November 1, 2012

U.S. Senate Committee on Health, Education, Labor and Pensions
Kathleen Laird on behalf of Chairman Tom Harkin (D-IA)
Grace Stuntz on behalf of Ranking Member Michael Enzi (R-WY)
Washington, DC

[Submitted electronically to: Kathleen_Laird@help.senate.gov and
Grace_Stuntz@help.senate.gov]

**RE: Questions to Stakeholders Regarding Appropriate Regulations of Pharmacy
Compounding**

Dear Members of the Senate Committee on Health, Education, Labor and Pensions and Staff:

The American Pharmacists Association (APhA) appreciates the opportunity to provide feedback to the U.S. Senate Health, Education, Labor & Pensions (HELP) Committee on its questions to stakeholders regarding appropriate regulations of pharmacy compounding, requested on October 26, 2012.

APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings and the uniformed services.

Despite news stories that continue to blame “compounding”, the tragedy that continues to unfold from the apparent large scale unauthorized and unlicensed manufacturing in Massachusetts was not the result of poor compounding. Rather, the manufacture and distribution of large quantities of sterile products to non-patient recipients for resale or administration in multiple states is just that – manufacturing. The pharmacists of America are prepared to support legislators and regulators in our collective desire to promote enhanced public health and safety.

APhA policies, established through a rigorous and broad based consensus process in the APhA House of Delegates address the differences between compounding and manufacturing. Following is APhA’s policy on compounding and the need for standards and an accreditation process to promote those standards:

2008 Pharmacy Compounding Accreditation

1. APhA reaffirms the 1992 Compounding Activities of Pharmacists policy, which states that compounding pursuant to or in anticipation of a prescription or diagnostic preparation order is an essential part of health care that is the prerogative of the pharmacist.
2. APhA supports compounding as defined by the Pharmacy Compounding Accreditation Board (PCAB) as a means to meet patient drug therapy needs.
3. APhA opposes compounding when identical medications are commercially and readily available in strength and dosage form to meet patient drug therapy needs.
4. APhA asserts that compounding is subject to regulations and oversight from state boards of pharmacy. APhA urges state boards of pharmacy to identify and take appropriate action against entities who are illegally manufacturing medications under the guise of compounding.
5. APhA supports accreditation of compounding sites by PCAB to ensure patient safety. APhA encourages state boards of pharmacy to recommend accreditation for those sites that engage in more than basic non sterile compounding as defined by PCAB.
6. APhA supports the development of education, training and recognition programs that enhance pharmacist and student pharmacist knowledge and skills to engage in compounding beyond basic, non-sterile preparations as defined by PCAB.
7. APhA encourages the exploration of a specialty certification in the area of compounding through the Board of Pharmaceutical Specialties (BPS).
(JAPhA NS48(4):470 July/August 2008) (Reviewed 2009)(Reviewed 2011)

Compounding is an integral part of the pharmacy profession and was virtually synonymous with the practice of pharmacy for many years prior to the inception of large-scale and wide-spread pharmaceutical manufacturing. Compounding continues as an important part of pharmacy practice that meets patient needs in hospitals, nursing homes, and many community settings. Compounding also allows patients with unique medical needs to have access to vital medications when commercially available medication dosage forms are not available for pharmacists and physicians to use for their patients. Common examples where compounding serves a critical patient need includes preparing dosage forms to enhance medication administration and adherence, preparing a formulation that excludes an ingredient known to trigger a patient's specific allergic response, maintaining a patient on a medication when there is a drug product shortage, and providing a drug product in a specific and customized strength or dosage form. In addition, cancer patients with challenged oral intake may require oral medications compounded into other dosage forms that meet that particular patient's needs.

Our utmost concerns are patient safety and access to best treatment options and access to quality medications, including appropriate compounded medications. Pharmacists who compound according to recognized professional standards and guidelines and state regulations help patients meet therapy goals and improve patient health and care outcomes. There continues to be an appropriate place for customized compounding of medications in today's health care system.

The practice of pharmacy compounding is regulated by state boards of pharmacy with FDA oversight for the medication ingredients used for compounded products and regulating manufacturers. Pharmacists engaged in compounding are expected to follow appropriate procedures for the types of products that are compounded. In the case of injectable medications,

specific procedures, tests and standards to ensure the sterility and integrity of the compounded product already exist. The United States Pharmacopeial Convention (USP) outlines standards for sterile compounding that must be followed regardless of practice setting.

APhA is committed to our longstanding work with state boards of pharmacy, FDA, Congress, our colleague pharmacy organizations, physicians, and other stakeholders in ensuring good compounding practices and standards are enforced to ensure patient safety and patient access to appropriately compounded products. We support the Committee's efforts to address compounding oversight and regulatory authority and would appreciate the opportunity to be a resource for the Committee as compounding discussions evolve.

APhA offers feedback on the following questions submitted by the Committee (*italics added to questions*):

Senate HELP Committee

Questions for Stakeholders Regarding Appropriate Regulation of Pharmacy Compounding

To help us better understand current federal and state oversight of pharmacy compounding, any gaps that may exist, and the possibilities for and implications of any potential legislative solution, we invite you to provide written answers to the following questions. These questions should not be read to indicate intent to offer legislation addressing any particular issue discussed herein. We would appreciate feedback by **5pm on Wednesday, October 31st**. Please send written responses to Kathleen Laird in Chairman Harkin's office (Kathleen_Laird@help.senate.gov) and Grace Stuntz in Ranking Member Enzi's office (Grace_Stuntz@help.senate.gov). [Note: Deadline was extended to Friday, November 1st.]

- **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?*

While not all the facts have been established, based on our understanding of the situation, both the Massachusetts Board of Pharmacy and FDA had the respective regulatory authority to act on compliance concerns and previous warning letters. From all reports the New England Compounding Center (NECC) was in violation of a myriad of existing laws and regulations. These violations are the apparent cause of the cascade of issues that resulted from distribution of products created by NECC. In addition, as evident in reports on this case, it appears that the company crossed the line from traditional pharmacy compounding (regulated by boards of pharmacy) into manufacturing (regulated by FDA) but clear and existing regulations were not invoked and enforcement options may not have been pursued. While it does not diminish the magnitude of the transgressions by NECC in the case, we are concerned that the lack of resources related to staff, inspectors and inspector education/training for either FDA or the Board of Pharmacy authority to act on such concerns and perform follow-up inspections contributed to lack of enforcement and patient safety issues. Due to

budgetary constraints, we see many state boards without the resources to conduct even cursory inspections of pharmacies, let alone having the expertise to inspect specialized facilities that prepare sterile products. We support increased resources for state boards and the FDA to enforce existing laws.

In order to fix a problem, it is important to clearly understand the root cause of the problem. We believe that it is important to clearly understand what occurred in this case prior to enacting any changes in the law. At this point in time, it appears that in this case current law, if adequately acted upon, would have been sufficient. While APhA is fully supportive of making sure that nothing like this occurs again, we are concerned that overreaching changes to the law could inadvertently block patient access to needed compounded medications. APhA welcomes the opportunity to continue to work with policy makers to strike an appropriate balance between preventing what occurred in this case while still maintaining the availability of compounded medication to patients who need them.

- *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?*

There continues to be challenges and uncertainties regarding pharmacy compounding oversight due to the unclear status of FDCA Section 503A requirements for exemption from provisions related to drug adulteration, misbranding, and approval. Because the Section 503A restriction against advertising and soliciting compounded drug orders was ruled unconstitutional by the courts, but not severed from the remaining requirements, we continue to hear concerns from pharmacists about FDCA implications and its impact on the long standing pharmacy practice of compounding to meet patient specific medication needs.

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

Yes, every state addresses compounding in statute and in regulations promulgated pursuant to the pharmacy practice act in each state. As a general rule, these laws do not need to be clarified to ensure accountability. Accountability will be increased by more resources and better training to enforce these laws. And, adherence to standards will also enhance accountability.

Compounding is performed according to defined standards and within the triad relationship of the physician, pharmacist and patient working together to individualize care for maximum patient benefit. There are different types of compounding that range in complexity and possibility of risk to the patient. Increasing complexity does not necessarily equate to increased danger to the patient since even a routine compounding of a drug to be injected into the spinal fluid can be high risk. Thus, on this spectrum sterile compounding, regardless of complexity, requires the most care, precaution and necessary safety measures in the process of compounding. At a

minimum, we recommend consideration that all states should require licensed pharmacies to follow USP 795 nonsterile compounding and USP 797 sterile compounding standards depending on the types of compounding they are performing, and that states should consider requiring a separate license and inspection for sterile compounding.

APhA also supports efforts to improve compounding training to better ensure consistency across states. Such efforts could focus on standardized training for state pharmacy board inspectors related to standards for compounding, and better guidance/training on differentiating between traditional compounding practice versus activities that suggest manufacturing. Efforts should also focus on the need for appropriate resources to fund and implement existing state board regulations, requirements, training and inspections. In addition, several state boards of pharmacy utilize non-pharmacist inspectors to inspect complex activities within various practice settings. We believe pharmacists with experience performing sterile and complex compounding should be utilized in inspecting all practice sites performing higher level of compounding activities.

Importantly, to protect public safety, statutory and regulatory requirements applied to licensing of compounding pharmacy should be applied equally and uniformly to other practice settings that also compound such as physician offices and ambulatory care settings. This is especially true for any person or entity engaged in sterile compounding.

- **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?

Yes, the legal status of FDCA 503A should be further clarified to create a uniform set of requirements and to afford better understanding and implication of its requirements on compounding practice in all practice settings. At a minimum, before a decision is made to enact 503A formally (without the unconstitutional provisions regarding advertising and promotion) we recommend a process be in place allowing affected parties the opportunity for comment to avoid unintended consequences.

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

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

Maintained. Allowing anticipatory compounding in preparation for expected prescription orders allows for process efficiencies and timely provision of medications. The volume of medication prepared should be reasonable, and prepared and stored in accordance to established guidelines. Again, often this is a patient access issue. Unduly curtailing anticipatory compounding may limit patient access to necessary medications without any increase in safety. For example, dermatologists often have

topical preparations that need to be compounded by a pharmacy. With the busy volume of most pharmacies, the minimal reimbursement on these prescriptions and often small amounts dispensed, many pharmacies would simply not create the product if they could not make it in large enough quantities to meet short term anticipated prescription orders.

It should be noted that in the NECC case, curtailing the volume of compounding would have undoubtedly affected the scale of the harm that was. The same problems may have occurred, but would have been more limited in scope. Compounding a single dose of a drug for injection in a highly contaminated environment is still problematic for the one patient who receives it. It may be prudent to limit production of sterile products. However, limiting the volume of doses of topical preparations may have little impact on safety.

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

Maintained. APhA policy does not support compounding when identical medications are commercially and readily available in strength and dosage form to meet patient therapy needs. However, there must be allowances for compounding of drugs in shortage when commercially available products are not immediately available or have been pulled from the market.

- *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?*

We recommend clarifying the purpose of a cap and the intended outcome of such cap. It is important to remember that there are times when interstate shipment of a compounded product is necessary because the product may not be available from an in-state pharmacy due to complexity of compounding method or other issues. Waivers should be available to this restriction for a defined period of time, when a public health imperative has occurred. Additionally, interstate is not necessarily distant. Many pharmacies serve patients in contiguous states, for example.

- *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?*

Increased communication and coordination among state boards of pharmacy and FDA is beneficial to patient safety and to improved transparency/awareness of regulatory activity and authority. We recognize that FDA and many state boards have resource challenges that impact inspection capacities and may benefit from having an option for an MOU. If the MOU provision remains, and states and FDA choose to enter into such agreements we recommend clarification if FDA would then provide education

and training for those state boards and if such agreements would be standardized across states.

- **Good Compounding Practices:**

Should there be a federal requirement for compounding pharmacies to comply with USP standards for pharmaceutical compounding? Are there other standards that would be more appropriate? 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?) How could federal good compounding standards be enforced?

APhA reiterates our support for requiring USP Standards 795/797 for all states as compounding is regulated at the state level. Regarding general standards, consider utilization of existing accreditation programs that could be used as references and resources, such as the Joint Commission (JC) and the Pharmacy Compounding Accreditation Board (PCAB). In addition, consider if USP might be interested in the development of additional standards through a consensus process using expert panels.

The practice of pharmacy compounding is regulated by state boards of pharmacy with FDA oversight for the medication ingredients used for compounded products and regulating manufacturers. Pharmacists engaged in compounding are expected to follow appropriate procedures for the types of products that are compounded. In the case of injectable medications, specific procedures, tests and standards to ensure the sterility and integrity of the compounded product already exist. USP outlines standards for sterile compounding that must be followed regardless of practice setting.

In addition, many compounding pharmacies earn or can earn accreditation through PCAB, a standards body that maintains and updates standards that reflect contemporary best practices. PCAB provides compounding practices an opportunity to compare their practices against national standards and achieve accreditation that provides consumers an indicator of quality practice. These standards are in place and regularly updated. To date, a limited number of compounding pharmacies have chosen to pursue accreditation. However, this recent public health issue has raised PCAB's profile, and interest is growing in the pharmacy community.

We do recognize the benefit of consistency across states for same level of extra requirements for practice above basic level of compounding. We would support consideration of enhanced standards and licensure for sterile compounding to ensure consistent standard across all states and providers in various practice settings. We also recommend consideration of federal good compounding standards and enforcement.

Virtually, every pharmacy in the United States compounds something at some point in time. Given the scope of FDA duties already, combined with a lack of resources, expecting FDA to inspect every pharmacy that does any compounding is simply unrealistic. Thus, providing a logical basis for the appropriateness of the distinction between compounding (regulated at the state level) and manufacturing (regulated by FDA) is necessary. More vigilance by FDA in determining when the line is crossed into manufacturing and stepping in to enforce current

law when it is appropriate is more realistic that giving FDA an enforcement mandate they cannot ever realistically meet.

- **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? 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.

As stated previously, there are sound reasons for allowing batch compounding in anticipation of prescription orders. Unduly curtailing this practice may often also curtail patient access without appreciably increasing safety (e.g. compounding many dermatological products). Again, this is a balance between safety and patient access. The root cause of a patient safety problem is not necessarily a function of the volume of drugs created or shipped across state lines, although poorly made sterile products shipped to multiple locations increase the public health risks over more limited distribution. The scale of the operation is simply one indicator of whether or not an entity has moved from being a pharmacy that is compounding and into manufacturing. Instead, safety issues are more attributable to the type of drug that is compounded (e.g. injectables) and the vigilance of regulators enforcing laws that already exist. The risk to the public is a function of the type of drug product being created and how it is administered combined with the vigor of compliance activities by regulators. If a pharmacy becomes a manufacturer, APhA supports them being regulated by FDA as a manufacturer. We would welcome further discussions on how to clarify and sharpen the demarcation between compounding and manufacturing and providing resources for appropriate enforcement.

We support consistency across state lines for criteria used to distinguish compounding from manufacturing. In addition, distinctions are needed as to what level or complexity of compounding is being done in addition to considerations of quantity of compounded products being distributed. Given the variety of traditional compounding services that are established elements of pharmacy practice, we would recommend that the Committee distinguish its intent. Is the goal to further regulate traditional compounding services? Is it to enhance regulation for sterile compounding? Is it to enhance regulation of high volume products being distributed from a practice setting? Each of these scenarios would be impacted differently by additional/clarified regulation.

- **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?

APhA could support a distinction between sterile compounding and other types of compounding. State regulations should be clear on what is compounding versus manufacturing and these regulation should be enforced by fully funded and well trained agencies. Compounded medications should be created pursuant to or in reasonable anticipation of a valid prescription and not otherwise be available commercially.

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

Typically, states rely on each other to regulate pharmacies within their borders and do not inspect pharmacies in other states. Thus, out of state residents are reliant upon the board of pharmacy in the state where the pharmacy exists to regulate compounding activity. Enforcement disparities may exist due to lack of resources or training. Thus, we urge adequate resourcing and training of existing regulatory authorities rather than broadening the reach and responsibilities of already overstretched regulators. Again, the problems in the NECC case appear to have been known to regulators but existing law was not fully enforced. Hindsight is 20/20. We suggest the fix is not to ask the regulators to try harder. Rather, in addition to clarifying the line between manufacturing and compounding, we believe state pharmacy license fees need to stay with state boards of pharmacy so they have the proper resources to inspect and enforce existing laws.

If a pharmacy is participating in substantial interstate compounding, a potential solution for better ensuring consistency across states may be either to establish standards that boards can rely on or to have some degree of FDA oversight. Current regulations for mail-order and central-fill pharmacies may be helpful models to consider.

- **Ingredients in Compounded Products:**

What, if any, federal regulations should there be 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? Should the use of marketed unapproved drugs be permitted in compounding?

This question must be answered through the prism of patient safety. For bulk ingredients, consider utilization of existing reference to USP standard products. The challenge with referencing an FDA-approved ingredient is that ordering of ingredients/products is by National Drug Code (NDC) number that does not indicate FDA-approval of the product. In addition, reference to a bulk ingredient being from an FDA-registered facility may not be

readily accessible in various ordering processes. If significant restrictions are applied, availability of bulk ingredients that meet USP standards that come through FDA-registered facilities may be impacted.

Overall, we support FDA's Unapproved Drug Initiative to remove unapproved products from the market, and FDA's work with CMS to ensure that the Medicare Part D prescription drug benefit is paying for FDA-approved medications. We will continue to work with the agencies on such efforts. However, given the number of unapproved ingredients on the market, and the lack of an efficient and/or clear way to identify FDA approval of a product, we would recommend considering USP as the reference and, requiring the use of ingredients meetings USP standards. We welcome further discussion with you regarding safe guards to ensure that high quality and safe ingredients are available.

- **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? If registration or listing is required, what fields of information should be included? Should firms subject to registration or listing pay a modest fee to cover FDA's costs of establishing the registration or listing program? Are there requirements associated with traditional registration or listing that would or would not be appropriate for entities engaged in compounding?

Community pharmacies are regulated by state boards of pharmacy and have a license that covers basic compounding practice. We have concerns with the utility of having every pharmacy register with the FDA and believe instead that the public would benefit from greater adoption of PCAB standards. There may be utility in first establishing different categories for licensure beyond basic non-sterile compounding in modest quantities, and then to provide appropriate inspections with qualified inspectors. At some point, at the other end of the spectrum, where sterile product preparation is occurring in large quantities for sale to others than individual patients, we might consider FDA registration appropriate.

Overall, we recommend considering that all practices performing sterile compounding should undergo compounding specific accreditation or be subject to inspection by state board or FDA inspection (if shipping large quantities). At a minimum, all states should require adherence to USP 797 standards for sterile product compounding.

We welcome the opportunity to offer additional insights and offer any resources we have.

- **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?

See previous commentary regarding the need and desirability of compounding in batches in reasonable anticipation of prescriptions.

Compounding is performed in response to a prescription or reasonability anticipated prescription from a licensed prescriber for an individual patient, which allows pharmacists to use their extensive medication knowledge and expertise to produce individualized medication formulation that meet established therapy goals, patient's needs and improve health outcomes. Compounded products should be labeled as such and prescribers and patients need to be aware that the product is compounded by the pharmacy.

There is no reason for a prescriber to call for the prescription to be compounded in the prescription order. APhA believes that if the drug is commercially available then compounding is inappropriate. Therefore, as stated before, the decision to compound is a triad relationship between the prescriber, pharmacists and patient.

We welcome the opportunity to offer additional insights and offer any resources we have.

- **Office Stock:**

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

- *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?*
- *Should the amount of product compounded for office stock be limited or capped in any way?*
- *Should there be specific labeling requirements for compounded product for office use?*
- *Should there be an allowance for compounding for research, teaching, or chemical analysis and not for sale or dispensing?*

Federal requirements and standardization for compounding for office use would improve transparency, allow more consistency across states, and ensure standardized and appropriate labeling for such products to improve transparency. We support the use of compounded medication being dispensed to prescribers for office use, where applicable state law permits. However, office use does not include prescribers reselling compounded medications or to date, processing office use as filled prescriptions orders. We further recommend focus on not allowing resale of office stock. We favor this over caps on office stock. We also favor appropriately labeled office stock. In addition, it may be beneficial to have office stock regulated and inspected by boards of pharmacy or boards of medicine adhering to the same requirements that exist for pharmacies.

Increasingly, compounding pharmacies rely on published formulas or "recipes" with documented shelf life or expiration date tests available. No product should be dispensed for resale or office stock without a well-documented expiration date. State boards or FDA could recognize certain publications as appropriate sources for these data.

In addition, APhA supports continued allowance for compounding for research and teaching as schools of pharmacy and other training facilities need continued opportunity to integrate compounding practice into their curriculums.

- **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)? Does it matter if the drugs at issue are not copies of commercially available drugs? How do the answers to these questions impact how office stock should be regulated? How do you define standardized drug products?

In general, if a product is commercially available and is not in shortage it should not be compounded. Furthermore, if a product is not being compounded for a patient specific issue (such as allergy to ingredient in commercially available product) then it should not be compounded. Compounding continues to play an important role in ensuring patient safety when a customized drug product is necessary. In addition, pharmacies should be legally allowed to compound products to help alleviate drug shortages during the period that the shortage exists and for a reasonable time after.

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

The FDA should have the authority to inspect if a pharmacy crosses the line into manufacturing. Ideally this "line" would be drawn in advance to avoid surprises. Pharmacies that are also manufacturing should know in advance if they are subject to FDA inspection.

- **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?

A label requirement indicating that a product was compounded would help improve transparency, prescriber understanding, and patient awareness and safety. Until experience is gained with this notification, flexibility should be allowed for pharmacies to meet the requirement until best practices are identified.

- **Adverse Event Reporting:**

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

We support reporting of any adverse drug events to FDA and support increased awareness and utilization of FDA's MedWatch program to report such events. We have worked with FDA as they continue to improve the MedWatch reporting forms, Web site, and processes. We do not see a need for specific requirements for compounded products as such reporting falls within the existing scope of reporting adverse drug events (ADE). Separately, APhA has supported the PDR Network's RxEvent reporting system and would like to see voluntary reporting of ADE simplified.

- **Federal and State Coordination and Communication:**

How well do federal and state officials coordinate existing authorities? 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? Should there be a specific federal requirement to coordinate enforcement and regulatory activities with respect to compounding pharmacy with state officials?

Patient care would be improved and regulatory duplication and burden would be reduced by communication and coordination. In addition, transparency would be enhanced. Compounding provides a great benefit to patients. Problems are avoided, and benefits maximized with open communications. Additional education and resources are needed. Education should be standardized including agreed upon terminology and approaches to inspections and enforcement to alleviate confusion. In addition, resources should be allocated to FDA for a public education campaign to inform and empower patients.

Please also comment on any other issues or buckets of issues that you think the Committee should consider when examining this topic.

Care should be taken to not create a legal and regulatory framework that has unintended negative consequences. For example, special consideration should be given for hospitals since they compound in every state, every day and in nearly every community. In addition, compounding by nuclear pharmacists is routine and could be adversely affected if any law does not take into considerations their special circumstances.

It is also important to note that compounded products are often necessary to address shortages or when products are no longer available from manufacturers and in these circumstances the compounding is done to ensure patient access to much needed medications. Our policies, listed above address this issue.

Thank you for the opportunity to provide comments on this important issue. If you have any questions or require additional information, please contact Brian Gallagher, BPharm, JD, Senior Vice President, Government Affairs at bgallagher@aphanet.org or by phone at (202) 429-7533.

Sincerely,

A handwritten signature in black ink that reads "Thomas E. Menighan". The signature is written in a cursive, flowing style.

Thomas E. Menighan, BPharm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO

cc: Brian Gallagher, BPharm, JD, Senior Vice President, Government Affairs
Marcie Bough, PharmD, Senior Director, Government Affairs