February 3, 2014

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

[Submitted electronically to www.regulations.gov]


Dear Sir/Madam:

APhA is pleased to submit these comments regarding the draft guidance on the Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act (the “Guidance”). Founded in 1852 as the American Pharmaceutical Association, APhA 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.

APhA appreciates the FDA’s rapid response to the passage of the Drug Quality and Security Act (“DQSA”) with the prompt release of new guidance related to compounding. While we acknowledge that developing guidance that provides sufficient detail and flexibility is challenging, such guidance is essential to pharmacists and compounding pharmacies that provide an indispensable service to patients. Although the Guidance provides a reasonable starting point for an oversight framework, we believe more precise definition of terms and additional detail are necessary. Below, APhA outlines the areas where we recommend additional FDA clarification.
I. Traditional and Office-Use Compounding:

APhA understands that the FDA has committed to providing additional guidance related to office-use compounding. Specifically, APhA’s understanding is that such guidance will indicate that State boards of pharmacy will retain responsibility for the regulation of office-use compounding. However, until that guidance is made available, pharmacists/pharmacies have no choice but rely on this Guidance when performing traditional compounding functions. As such, it is imperative that compounding pharmacists are provided with clear and reasonable direction regarding the FDA’s expectations related to such compounding.

Based on the FDA stakeholder call on December 3, 2013, as well as numerous statements made by members of Congress during the deliberation of the DQSA, APhA expects that the Guidance will not result in fundamental shifts in enforcement related to traditional compounding. Specifically, APhA anticipates that pharmacists and pharmacies engaged in traditional compounding will continue to be regulated by State boards of pharmacy provided that they comply with the appropriate provisions of the Guidance.

However, certain Guidance provisions require additional clarification. For example, the Guidance sets forth a number of conditions that must be met in order for pharmacists to compound before the receipt of a patient-specific prescription. Specifically, the Guidance requires that any such compounding is done under the auspices of an “established relationship” between a pharmacist and a prescriber (p. 3, line 99). Our members have expressed concern that it is unclear how the FDA will interpret this term. Does established relationship merely mean that the pharmacist and the prescriber know each other? Will the FDA allow State boards to determine this? Given that the majority of States allow pharmacists to sell compounded drug products to physicians for office-use, many States already have interpretations of an appropriate “established relationship” between a pharmacist and a physician. Relying on current State law would ease compliance for compounding pharmacists and would ensure uninterrupted patient and provider access to compounded medications. APhA strongly encourages the FDA to offer additional detail regarding the definition of “established relationship” and, where available, to defer to existing State law.

Additionally, APhA has a similar concern with the term “inordinate amount” (p. 4, line 136) as it applies to “commercially-available” (p. 4, lines 136-137) products. As previously stated, pharmacists wish to comply with the Guidance, but our members are concerned that the language provided does not offer sufficient detail. For instance, is “commercially-available” defined to include drug products listed on the Current Drug Shortages Index

---

1 Statement of Jane Axelrad during the December 3, 2013 call regarding the release of the Guidance.
2 Statement of Rep. Tom Coburn, Congressional Record (Nov. 18, 2013)(“There has been a lot of concern that by reaffirming Section 503(a) of the Food, Drug, and Cosmetic Act, office-use compounding of drugs is not recognized as a permissible compounding activity. Therefore, I want to make clear that this legislation does not change current law or authority over the dispensing or distribution of medications by pharmacists, compounded or manufactured, for a prescriber’s administration to or treatment of a patient within their practice.”); Statement of Sen. John Boozman, Congressional Record (Nov. 18, 2013) (“The practice of pharmacy, including pharmacy compounding, is a state issue. Nothing in this law changes that. Compounded drugs for office-use is a state issue. Nothing in this law changes that.”).
If, in response to a situation that threatens patient safety and needs, such as a regional drug shortage, a pharmacy experiences a spike in the compounding of the drug in shortage, would that spike be considered an “inordinate amount”? We ask that FDA consider revising this language to include clearer limits on what would be considered appropriate and, preferably, to defer to State boards of pharmacy in determining such limits. As indicated above, our understanding is that FDA has no intention of changing its enforcement patterns regarding traditional compounding. Nevertheless, because the Guidance includes new information, clarification would be highly beneficial for providers who want to ensure that they are in compliance with FDA expectations while still maintaining patient access to compounded medications.

II. Limits on Interstate Distribution

APhA has a number of concerns associated with the limits the Guidance places on the interstate distribution of compounded drug products. Our members have highlighted specific concerns related to the 5% limit on interstate distribution (p. 5, line 151) as well as the Memorandum of Understanding (MOU) between the FDA and the states. We address each in turn below.

A. 5% Limitation

APhA strongly encourages the FDA to reconsider the inclusion of the 5% limitation on compounded drug products as the default “non-MOU” metric. We ask that the FDA clarify how it will calculate “total prescription orders” (p. 5, line 151). Is this calculated on a monthly, quarterly, or annual average basis? How is the baseline established, and if there is temporary spike (e.g., for a drug in shortage), how would it affect a pharmacy’s compliance? Further, because the FDA has failed to provide any basis for this number, the 5% limit appears arbitrary, at best. Additionally, enforcing this limitation could result in hardship for patients who trust and rely on specific pharmacists/pharmacies for their compounded drug products, especially patients who live near state borders. For example, in a small pharmacy, a single pharmacist may not fill a large number of prescriptions, thus the number of compounded drug products it takes to reach the 5% limit is relatively small. For example, if a pharmacist located on the Ohio/Pennsylvania border only fills 100 compounded prescriptions a month, that pharmacist can only distribute 5 of those prescriptions to out-of-state patients. In order to ensure that he/she is treated as a traditional compounding pharmacist under 503A, the pharmacist may have to turn away customers with compounding needs. In certain areas, particularly rural counties, it may be very difficult for patients to find another compounding pharmacist with the capacity to provide the necessary prescription.

Furthermore, even in more populous regions, the 5% limitation may result in access issues. For example, there is currently a single accredited compounding pharmacy in Leesburg, Virginia. Many patients who rely on the pharmacy for compounded medications live in Maryland and the District of Columbia, and the 5% limitation on interstate distribution would create significant compliance issues for the pharmacy. The Guidance provides no justification for the 5% limitation and cites no data or studies linking a higher volume of out-of-state sales of

---

compounded drug products to unsafe practices or an increased risk to patient safety. Thus, to ensure patients continue to have unimpeded access to products compounded safely under 503A, APhA respectfully suggests that the FDA reconsider the 5% limitation and instead continue to work with stakeholders to identify a more effective method for ensuring the safety and availability of high-quality compounded drug products.

Further, we note that the imposition of arbitrary percentage limitations on interstate distribution of compounded drug products does not harmonize very well with the more general guidance on traditional compounding, which focuses on the established or historical relationship between a prescriber and a pharmacist to determine the relative risk associated with compounding. APhA supports all efforts to increase drug safety and reduce risk to patients, but we also believe that the requirements for compounding should be consistent when possible. Thus, we request that the FDA consider compounding at both the intra- and interstate levels in the context of the patient-prescriber-pharmacist triad.

B. Memorandum of Understanding

APhA has concerns regarding the MOU between the FDA and the States. First, while APhA appreciates the fact that the FDA will not enforce the 5% limitation until 90 days after the MOU (p. 6, lines 210-212) has been finalized and sent to the States for consideration and signature, this does not provide a clear timeline for enforcement. Does this mean that FDA will enforce the default limit as soon as the MOU is provided to states? State processes for considering the MOU will differ, therefore 90 days may not offer sufficient time for States to fully consider the MOU, much less establish the necessary regulatory framework for implementation. Therefore, to avoid confusion and patient access issues that could result from regulatory volatility related to changes to compounding requirements, we respectfully request that the FDA consider extending the timeline to 120 days.

APhA notes that the Guidance does not set forth a process for comment on the MOU. We strongly encourage the FDA to promulgate the draft MOU subject to comment, to provide an opportunity for all stakeholders, including but not limited to the National Association of Boards of Pharmacy (“NABP”), State boards of pharmacy, and pharmacists to offer input. APhA recognizes that FDA is moving as quickly as possible in developing the MOU, but we also respectfully suggest that the FDA refrain from using the 1999 MOU as a starting point for development. Many of the issues that were highlighted in that MOU would still be of considerable concern today. Specifically, the 1999 MOU included percentage limitations on the amount of compounded drug products that may be distributed interstate. States-- and particularly State boards of pharmacy, which are the recognized regulators for the pharmacy profession-- should be have the discretion to work cooperatively with the FDA to determine the most effective method for the regulation of drug compounding and the distribution of such compounded drug products to out-of-state patients. We urge the FDA to work with States to develop the most appropriate control on a State-by-State basis, rather than applying arbitrary limits that may impede patient access to vital compounded drugs.

The provision of safe, effective medications, including compounded medications, is of paramount importance to APhA’s members and we support the FDA’s efforts to ensure drug quality and security. APhA hopes that our comments will be helpful and we look forward to continuing to work with the FDA regarding compounding and the dispensing of compounded drug products. We hope to be a resource for FDA and we are happy to be of assistance in any

5 See Addendum 1: APhA’s Comments to the FDA on the 1999 Draft Memorandum of Understanding.
way possible. Thank you for the opportunity to provide comments on this important issue. If you have any questions or require additional information, please contact Jillanne Schulte, Director of Regulatory Affairs, at jschulte@aphanet.org or by phone at (202) 429-7538.

Sincerely,

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

cc: Stacie S. Maass, Senior Vice President, Pharmacy Practice and Government Affairs
APhA Comments to FDA
Docket No. FDA-2013-D-1444-0001
February 3, 2014

Addendum 1: APhA’s Comments to FDA on the 1999 MOU
June 1, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher Lane
Room 1061
Rockville, MD 20852

RE:   Federal/State Memorandum of Understanding on Interstate Distribution of Compounded Drug Products; Docket No. 98N-1265

Dear Sir or Madam:

The American Pharmaceutical Association (APhA), the national professional society of pharmacists, is pleased to submit comments on the Food and Drug Administration’s (FDA) draft Standard Memorandum of Understanding (MOU) on Interstate Distribution of Compounded Drug Products. APhA’s 53,000 members include practicing pharmacists, pharmaceutical scientists, and pharmacy students.

Compounding, the preparation of individual medications for patients, has been a component of pharmacy practice dating back to the profession’s origins. Pharmacists who compound today provide medications for patients who require an alternative to commercially available products. Without these services, many patients would have difficulty finding medications that meet their medical needs.

APhA appreciates FDA’s initial attempt to develop this MOU for the interstate distribution of compounded drug products; however, APhA has concerns that the MOU must better honor the long-standing regulatory role of the state boards of pharmacy. The state boards of pharmacy are the recognized regulators for the profession of pharmacy – they effectively monitor and regulate the profession and demand high professional standards to protect the public.

By passing the Food and Drug Administration Modernization Act (FDAMA), Congress intended to “ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent small-scale manufacturing under the guise of
compounding.”1 FDAMA also sought to clarify the roles between the FDA and the states through the MOU to provide “for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such state.”2 (emphasis added).

APhA is concerned that the draft Standard MOU exceeds the scope authorized by the statute in two areas. Specifically, at no point does FDAMA call for the MOU to include investigation of complaints about products distributed within a state, nor to develop percentage limits on the interstate distribution of compounded products. The law requires the MOU to direct states to investigate complaints relating to compounded drugs distributed to patients outside the state where the products were compounded. The scope of the complaint section in the draft MOU is unclear but appears more broad than FDAMA’s narrow scope. The draft MOU further exceeds the requirements of FDAMA by placing percentage limits on the interstate distribution of compounded products. Although FDAMA outlines a default percentage limit for states that do not enter into a MOU, FDAMA does not require that the MOU include a percentage limit. In the current draft, states lose the discretion to define for themselves the most effective manner to regulate prescriptions that may be compounded and distributed to out-of-state patients by pharmacists.

Complaints About Compounded Drugs:
Congress sought to build partnering relationships between the federal government and the states under FDAMA. It appears that FDAMA never intended to define for the states their regulatory and enforcement roles. Within their jurisdictions, state agencies routinely inspect and monitor pharmacies for compliance with applicable state laws regulating the practice of pharmacy.

Section III(B) needs clarification and better organizational structure. The law specifically pertains to interstate distribution of compounded drug products by requiring the MOU between FDA and the states to provide “for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state.”3 The draft MOU’s subheading “Complaints About Compounded Drugs” for section III(B) on page 5 appears

---

to indicate a much broader scope. Moreover, the MOU’s explanation authorizing one state to investigate complaints “relating to compounded drug products distributed outside such State” does not appear until page 9 of section III(B), many pages after specifying the types of complaints that should be investigated. This organizational structure could cause some misinterpretation among those who might think this section of the draft MOU includes intrastate, rather than solely interstate, distribution of compounded products.

Section III (B) of the MOU should be clarified by changing its subtitle to “Complaints About Compounded Drug Products Dispensed or Distributed Interstate.” Further, the MOU’s explanation authorizing one state to investigate complaints “relating to compounded drug products distributed outside such State” should be moved closer to the beginning of the section for added clarification. Overall, the draft MOU should be limited to that defined in title and statute: compounded products distributed interstate.

Distribution of Inordinate Amounts of Compounded Drugs:
This section of the draft MOU defines for the state boards exactly what is an “inordinate amount” of compounded drugs – no more than 20 percent of prescriptions may be compounded and distributed interstate by a pharmacy. This percentage, however, is presented without any substantiation for the limit. What data substantiates this recommendation? Do studies exist to show that compounding activities above this limit are somehow inherently dangerous?

The arbitrary limit of 20 percent does not appear to be supported by FDAMA. Within Senate Report No.105-43, “‘Inordinate’ quantities means amounts typically associated with ordinary commercial drug manufacturing.” In defining “inordinate amounts,” the draft MOU uses percentages (20 percent) without providing justification and provides no comparison to the definition in the Senate report. The draft MOU fails to explain why any amount of compounded drug product distributed interstate, or outside the 50 mile radius allowed for “local” interstate distribution of compounded drug products, poses a threat to public health or demonstrates that a compounding pharmacy is “manufacturing in the guise of compounding.” The MOU unnecessarily establishes percentage limits on interstate distribution of compounded drug products that FDAMA does not require.
Under the conditions of the draft MOU, a pharmacist who dispenses 52,000 prescriptions annually – 1,000 prescriptions weekly – may distribute approximately 10,400 compounded prescriptions annually – 200 compounded prescription weekly – interstate. Should the pharmacist dispense 10,401 prescriptions, the pharmacist is violating the limits set in the draft MOU. Is the 10,401 prescription somehow less-safe than the other compounded products? How does 10,401 prescriptions compare with the output of a commercial drug manufacturer? It is difficult to argue that a pharmacist who distributes more than the percentage limits is conducting commercial drug manufacturing in light of commercial pharmaceutical manufacturers multimillion dollar annual sales of prescription drugs.

APhA is concerned that the draft MOU will require state boards of pharmacy to accept unnecessary federal regulatory intervention that circumvents the board’s authority to regulate the profession. The draft MOU forces state boards of pharmacy to embrace its definition of what constitutes “inordinate amounts” of compounded drug products distributed interstate. “Inordinate amounts” should not be defined in terms of strict percentages. The specific ceilings established in the draft MOU demonstrate no correlation between the practice of medicine, pharmacy, public health, or the patient’s need for compounded prescriptions. Patients may find themselves endangered if they are unable to attain the medications they need from compounding pharmacists.

There appears to be an assumption in the draft MOU that there is no regulation of compounding at the state level. Whether products are intended for intrastate or interstate distribution, the compounding of these products is subject to state practice act requirements. Some state practice act requirements already include or address a discussion of inordinate quantities. For example, the Washington state regulations detail: “The compounding of inordinate amounts of drugs, relative to the practice site, in anticipation of receiving prescriptions without any historical basis is considered manufacturing”. Washington state also maintains that the “distribution of inordinate amounts of compounded products without a prescriber/patient/pharmacist relationship is considered manufacturing.” It is unclear how Washington state’s definition, focusing on the prescriber/patient/pharmacist relationship, will square with the draft standard MOU’s arbitrary percentage limits.

---

4 Washington State BR. Ch. 246-878.20,30(3)
5 Washington State BR. Ch. 246-878.20,30(3)
The final MOU should recognize compounding in the context of the patient-prescriber-pharmacist triad. The final MOU should also allow the state boards of pharmacy to determine how best to regulate interstate distribution of compounded products without setting arbitrary ceilings.

In conclusion, APhA recommends the draft MOU respect the jurisdiction of state boards of pharmacy to protect the public within their states from harmful pharmacy practices versus enforcing arbitrary limits on interstate distribution of compounded drugs. State boards of pharmacy should have the authority to define “inordinate amounts” of compounded drugs based on their role and responsibility to protect public health within the context of good pharmacy practice regulations and state pharmacy practice acts. The final MOU should also allow state boards of pharmacy to determine the best means to investigate compounding pharmacists and pharmacies.

The members of APhA appreciate your consideration of these comments.

Sincerely,

[Signature]

John A. Sans, PharmD
Executive Vice President and Chief Executive Officer
To:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher Lane
Room 1061
Rockville, MD 20852