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February 3, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2013-D-1444; Draft Guidance; Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) on the draft guidance announced in the Federal Register on December 4, 2013.[i] The guidance would implement Section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) which regulates entities that compound drugs. On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law [P.L. 113-54]. The DQSA removed several parts of Section 503A that were declared unconstitutional by the U. S. Supreme Court in 2002. The law requires the FDA to go through the rulemaking process to implement several parts of Section 503A. ASHP offers these comments on the guidance that the Agency is proposing pending such rulemaking and selection, convening, and consultation with the Pharmacy Compounding Advisory Committee (the Committee).

ASHP is the national professional organization whose 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in acute and ambulatory care settings, including hospitals, health systems, and clinics. For more than 70 years, the Society has been on the forefront of efforts to improve medication use and enhance patient safety. As you are well aware, ASHP was actively engaged with the FDA and Federal lawmakers from the onset of the meningitis outbreak in the Fall of 2012. In the aftermath of the incident, ASHP has worked with policymakers, practitioners, and nationally recognized experts in compounding and manufacturing to develop new approaches to protect patients

from preventable harm, and to give practitioners and organizations confidence that compounding outsourcers are appropriately regulated and inspected, and that the products they produce are safe.

U.S. hospitals, which will be governed by Section 503A of the FD&C Act, prepare a vast array of compounded sterile preparations every day in order to meet the needs of patients. The majority of compounded medications hospitals utilize are prepared in-house by pharmacy departments. The compounded medications that hospitalized patients need span from simple intravenous admixtures to complex customized medications that are not available off the shelf, such as multi-ingredient cardioplegia solutions for heart surgery, precisely measured combinations of epidural pain medication and adult medications prepared in concentrations that can be safely administered to infants and children.

However, hospitals also enlist the help of outside compounding pharmacies for some compounded preparations for several reasons. For example, they may not have the necessary equipment or facilities to prepare some high-risk preparations, or they may face medication shortages for commercial products.

ASHP has dedicated itself to developing the highest standards for compounding and sterile product preparation in hospitals. The Society's guidelines on sterile product preparation formed the basis for the three-tier risk assessment structure later incorporated by the United States Pharmacopeia into Chapter 797, its standards for compounding sterile products. In 2010, ASHP published the ASHP Guidelines on Outsourcing Sterile Compounding Services to advise pharmacy departments on how to conduct due diligence when selecting outsourcing vendors. In addition, we have developed an assessment tool based on our guidelines that helps pharmacists in hospitals and health systems comprehensively evaluate sterile compounding service providers and use comparative data for their vendor selection process. Our guidelines and assessment tool are and have been available free as a public service to the health care community and others.

ASHP respectfully submits the following recommendations to the FDA on the Draft Guidance: Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act.

Page 3, lines 95 – 103:

2. *The compounding of the drug product is performed*
   - *By a licensed pharmacist or licensed physician in **limited quantities before the receipt of a valid prescription order** for such individual patient when:*
     - *the licensed pharmacist or licensed physician has historically received valid prescription orders for the compounding of the human drug product and*
     - *the orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either the patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order (sections 503A(a)(1) and (2) of the FD&C Act).*

ASHP is concerned that this clause of the regulation may potentially affect timely provision of sterile preparations to hospitalized patients. In these settings, compounded sterile injectables are typically prepared in limited quantities in advance to be on hand for emergencies or anticipation of patient need as the time needed to compound on demand may represent an unacceptable delay. These preparations are always dispensed pursuant to a prescription within the patient–provider–pharmacist relationship.

ASHP policy is "to affirm that extemporaneous compounding of medications, when done to meet immediate or anticipatory patient needs, is part of the practice of pharmacy and is not manufacturing."[ii] We request that the Agency consider guidance similar to that in CPG Sec. 460.100 Hospital Pharmacies - Status as Drug Manufacturer in which hospitals are exempted from registration and certain other requirements for manufacturers.[iii]

ASHP recommends that the agency clarify in its guidance on whether or not it will consider compounding for office use to be a matter for state boards of pharmacy. It is important that the FDA recognize the patient-safety enhancing role that hospital and health-system pharmacies serve in providing outpatient clinics and other ambulatory settings within their system with compounded products.

Page 4, lines 105 – 115

3. *The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding[5] using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.*

ASHP Policy 0616 is "to encourage pharmacists who compound medications to use only drug substances that have been manufactured in Food and Drug Administration-approved facilities and that meet official United States Pharmacopeia (USP) compendia requirements where those exist."

> [5] *After the Modernization Act was enacted in 1997, the USP moved its chapter on pharmacy compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.*

Footnote number five on page four may give the impression that USP Chapters <795> and <797> are the only applicable pharmacy compounding standards. Although USP <795> and <797> address nonsterile and sterile compounding respectively, a number of other USP chapters are relevant to pharmacy compounding, depending on the type of compounding, and should be observed. As mentioned in <797>, some are particularly critical for high-risk compounding and finished articles with beyond-use dating extended outside limits established in that chapter:

- <1163> Quality Assurance in Pharmaceutical Compounding
- <1176> Prescription Balances and Volumetric Apparatus
- <1035> Biological Indicators
- <1121> Sterilization and Sterility Assurance of Compendial Article
- <71> Sterility Tests
- < 85> Bacterial Endotoxins Test
- < 151> Pyrogen Test
- <1211> Sterilization and Sterility Assurance of Compendial Articles
- <1222> Terminally Sterilized Pharmaceutical Products-Parametric Release
- <1207> Sterile Product Packaging-Integrity Evaluation

ASHP requests that the FDA change the text of the current footnote to "Although USP <795> and <797> address nonsterile and sterile compounding respectively, a number other USP chapters are relevant to pharmacy compounding and are included under the term 'applicable chapters'".

In addition to official monographs, USP-NF Monographs for Compounded Preparations are also available from USP and may differ considerably from the official monographs.[iv]

The Society requests that the FDA address their position on the use of official USP monographs versus USP compounding monographs.

Page 4, lines 135 – 137

8. *The licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products (section 503A(b)(1)(D) of the FD&C Act).*

ASHP requests that the FDA define the terms "inordinate amounts," and "commercially available" as they implement the DQSA. The legislation does not define these terms and unlike The Food and Drug Administration Modernization Act of 1997, which initially inserted Section 503A into the FD&C Act, there is no accompanying report language for DQSA. The Senate Committee Report for FDAMA stated that it was the intent of Congress to mean that "'inordinate' quantities means amounts typically associated with ordinary commercial drug manufacturing."[v] ASHP recommends that the FDA define these terms only after they have consulted with the Pharmacy Compounding Advisory Committee and other relevant stakeholders.

ASHP policy is "to support the principle that medications should not be extemporaneously compounded when they are commercially and readily available in the form necessary to meet patient needs."[vi] ASHP members have reported that they compound copies of FDA-approved drugs as an emergency measure during shortages, particularly those of critically needed electrolytes and other drugs essential in the acute care environment. While these are compounds of FDA-approved drug products, they are not commercially available to ASHP members. These agents are intended solely for treating patients of the individual hospital or health-system and are dispensed pursuant to a patient-specific prescription.

Compounding from nonsterile ingredients is addressed in USP <797> under "High Risk Level CSPs." Compounded preparations must be terminally sterilized and absent sterility testing, storage periods may not exceed 24 hours at room temperature, three days under refrigeration, and 45 days in a frozen state.

ASHP recommends that hospitals operating under 503A may continue to meet urgent patient needs by high risk sterile compounding of shortage drugs using USP<797> standards. We anticipate that the volume produced by this activity will be limited by the short beyond use dating imposed by these standards and availability of compounded drugs from outsourcing facilities. We request that the Agency explicitly address the ability for a compounding pharmacy

to compound FDA-approved drugs under 503A that, for a variety of reasons, may be in short supply and are unavailable from the manufacturer or outsourcing facility.

While ASHP does not support using compounded alternatives to FDA-approved commercially available drugs for cost-saving, we recommend that the Agency work with the appropriate Federal agency to monitor the financial impact on the overall cost of care for patients who receive these products.

Pages 5 – 6, lines 160 through 194

1. Withdrawn or Removed List; 2. Bulk Drug Substances List; 3. "Demonstrable Difficulties" for Compounding List

ASHP supports FDA's development of a list of drug products that cannot be compounded because they have been withdrawn or removed from the market. However, the current list of these products is 15 years old and has not been updated since its development in 1999. The Society recommends that the FDA review this list and solicit public input in advance of Committee consideration at a public meeting.

ASHP also supports the limitation of substances used for compounding to those that do not present a known threat to public health. ASHP recommends that exact copies of proprietary dosage forms be prohibited in addition to the drugs themselves.

We also support FDA's decision to postpone enforcement of the list of drugs with demonstrable difficulties for compounding and the list of bulk drug substances that do not have an applicable USP or NF monograph and are not components of FDA-approved drugs. DQSA requires that the Committee be in place before these lists can be updated. ASHP intends to submit comments to the FDA on these proposed rules. We believe that these lists should be the first order of consideration by the Committee once representatives are selected and the Committee convened. As much has changed since the previous Committee discussed this topic, it will be important for them to consider information from pharmacists that have invested in technology that may remove some "demonstrably difficult" conditions.

Page 6, lines 196 – 212

4. *Memorandum of Understanding Between FDA and the States.*

Under section 503A(b)(3)(B)(ii), an individual or firm in a State that does not enter into an MOU with FDA that distributes, or causes to be distributed, compounded drug products out

of the State in which they are compounded, can compound for interstate distribution outside the state only 5% of the total prescription orders dispensed or distributed by the individual or firm. FDA does not intend to enforce the 5% limit on interstate distribution until 90 days after FDA has finalized an MOU and made it available to the States for their consideration and signature.

As interstate distribution quantities in states with multiple contiguous borders may exceed 5%, it is possible that imposing an across the board 5% upper limit may affect patient access to needed medications. ASHP recommends that pharmacy boards in such states be allowed to assess this risk and write their individual memoranda of understanding accordingly, including their plans to monitor and respond to complaints, in consultation with the Agency.

For states that do not choose to enter into an MOU, additional clarification of the basis from which the 5% will be calculated is needed. Ideally a denominator that is easily determined and readily retrievable should be selected. "Prescription orders" is not a recognized term in pharmacy practice. Pharmacies receive both prescriptions, which they dispense, and orders, which they fulfill. It is also important for the FDA to recognize the difference between distribution and dispensing in determining the 5% cap, and not include prescriptions dispensed across a state line towards a statutory cap on the percent of drugs distributed.

21 CFR 2083 clearly defines dispensing to patients as "the act of delivering a prescription drug product to a patient or agent of the patient" and distributing which "means the act of delivering, other than by dispensing, a drug product to any person." We urge the FDA to recognize that patient-specific prescriptions may be dispensed across a state line (e.g., in the case of pharmacists preparing infusion products for use in the home) and that these prescriptions should not be considered towards "inordinate amounts" of <u>distributed</u> drugs.

<u>Page 7, lines 246 – 247</u>

5. *The drug product's labeling, advertising, and promotion must not be false or misleading. (Sections 502(a), 502(bb), and 201(n) of the FD&C Act).*

Given the Agency's stated concerns and enforcement actions regarding compounded bio-identical hormone and autism therapies, ASHP suggests that additional guidance on identifying and reporting violations of Sections 502(a), 502(bb), and 201(n) be provided to state pharmacy boards.[vii]

The Society appreciates the opportunity to comment on the FDA's draft guidance. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,

Christopher J. Topoleski
Director, Federal Regulatory Affairs

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[i] Federal Register, Volume 78, No. 233. Pages 72901 – 72902

[ii] ASHP Policy 0616, *Safe and Effective Extemporaneous Compounding.*

[iii] http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074397.htm

[iv] http://www.usp.org/usp-healthcare-professionals/compounding/compounding-monographs/usp-nf-monographs-compounded-preparations

[v] U.S. Senate. Committee on Labor and Human Resources. *Food and Drug Administration Modernization and Accoutnabilyt Acto fo 1997: Report Together with Minority Views (S. Rpt. 105-43), P. 68.*

[vi] ASHP Policy 0616, *Safe and Effective Extemporaneous Compounding.*

[vii] http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm183088.htm#FDAsEnforcementAction