Department of Health and Human Services

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

February 5, 2013

Thomas Rasnic
Vice President, Quality, Regulatory, and R&D
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Two Conway Park
150 North Field Drive, Suite 350
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Dear Mr. Rasnic:

This responds to your January 11, 2013, letter to Heidi Marchand, Assistant Commissioner, Office of Special Health Issues, in which you request that the Agency send a letter to the New York State Board of Pharmacy in response to the January 3, 2013 letter from New York State Commissioner of Health and Commissioner of Education to Margaret Hamburg, M.D., Commissioner of Food and Drugs. You request that such letter reaffirm a statement in the January 27, 2005 letter to PharMEDium from Steven D. Silverman, Office of Compliance, Center for Drug Evaluation and Research. Specifically, PharMEDium asks the Food and Drug Administration (FDA) to reaffirm that the Agency remains willing to consider PharMEDium's approach to linking patients to the firm's compounded drugs after shipment to be an acceptable alternative to compounding drugs after receipt of a valid prescription for an individually identified patient. For the reasons discussed below, FDA is no longer willing to condition our exercise of enforcement discretion in the manner set forth in the 2005 letter.

As you know, FDA has advised PharMEDium that patient specificity is needed to align the firm's operations with that of a compounder rather than a typical drug manufacturer. Working with the Agency, PharMEDium proposed to address the need for patient specificity by conducting a pilot study designed to assess the feasibility of linking its compounded drugs to specific patients through the use of a barcode system. PharMEDium also submitted information regarding an alternate system for hospitals that are not barcode ready. Using these approaches, PharMEDium attempted to show the ability to link patients with the drugs they received after the drugs had been provided to the hospital for administration to patients but it was not equivalent to the firm receiving a valid prescription for an individually identified patient before distributing its compounded drugs to hospitals. FDA expressed willingness to exercise enforcement discretion on the patient specificity issue at that time. Letter to PharMEDium from S. Silverman dated January 27, 2005 ("at this time, we will consider the link as an acceptable alternative to drugs compounded after receipt of a valid prescription for an individually identified patient.").

It does not appear that PharMEDium has consistently implemented and maintained the conditions under which we were willing to exercise enforcement discretion—linking each of the firm's compounded drugs to specific patients who received them. During a September 2007 inspection of the PharMEDium's Sugar Land, Texas facility, firm management said it was the responsibility of the hospitals receiving the drugs to link them to patients and that PharMEDium

did not conduct surveillance of the hospitals to determine whether this was done. We note that patient linkage could not be established in November 2007, when FDA tried to follow up on adverse event reports after CDC notified FDA of 6 cases of *Sphingomonas paucimobilis* infections at a hospital in Maryland, and 2 additional cases in a California hospital. These infections may have been linked to a fentanyl IV made by PharMEDium at your Cleveland, Mississippi site, but, according to CDC, neither hospital was able to determine which lot of fentanyl the patients had received.

Furthermore, in a May 2008 meeting with PharMEDium, FDA discussed that PharMEDium's contract with hospitals describing the need to link patients to your firm's compounded drugs did not provide assurances that such links were made. In addition, FDA discussed the need to identify a corresponding lot number for a specific product received by a patient in case of emergency, as well as the importance of PharMEDium having a robust auditing program to ensure that hospitals can provide patient and lot-specific information within 24 hours. In a June 20, 2008, letter from PharMEDium to FDA, your firm committed to conducting effectiveness checks by surveying customers to determine the method of assuring links of compounded preparations to patients, and to performing in-person validations of hospital sites to visually review patient-linkage mechanisms. During a November-December 2010 inspection of your Sugar Land facility, investigators asked about patient specificity. In response, PharMEDium personnel noted that there was no linkage of the products to specific patients and that the firm compounded and shipped product to hospitals in advance of obtaining a prescription. Although investigators were told that every compounded unit bears a unique bar code to facilitate the tracking of each unit to particular hospitals, it would not provide a link to specific patients.

Whether a firm obtains patient-specific prescriptions is one of the factors that FDA considers in evaluating whether the firm is engaged in traditional pharmacy compounding versus manufacturing in the guise of compounding. Currently, there are conflicting judicial decisions regarding the applicability of section 503A of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353a, which exempts compounded drugs from several key statutory requirements if certain conditions are met.[1] Nevertheless, both section 503A of the Act and the agency's Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002),[2] which sets forth a non-exhaustive list of factors that FDA considers in determining what types of compounding might be subject to enforcement action, recognize that [traditional] compounding pharmacy

[1] *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) (holding that the solicitation and advertising prohibitions in section 503A are an impermissible regulation of commercial speech and that those provisions are unconstitutional and cannot be severed from the rest of section 503A, causing all of section 503A to be invalid); *with Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008) (compounded drugs are "new drugs" and "new animal drugs" within the meaning of the Act and therefore are subject to regulation by the FDA, and the advertising prohibitions in section 503A previously found to be unconstitutional can be severed from section 503A, leaving the remaining parts of that section valid and effective).
[2] *See* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm.

practice involves receipt of valid prescriptions for individually identified patients prior to distribution of a drug.[3]

The recent fungal meningitis outbreak that has been associated with over 40 deaths and 650 illnesses is the most recent and most serious in a series of adverse events associated with compounded drugs that have occurred in the last ten years. The Agency is particularly concerned about the large-scale distribution of compounded sterile drugs to health care facilities nationwide when compliance with appropriate standards for large-scale sterile production may not have been met, putting patients at risk.

These events have caused the Agency to reexamine its exercise of enforcement discretion with regard to the need for valid, patient-specific prescriptions. In particular, we are unable to reaffirm the statement in the January 2005 letter as you requested because we have determined that, going forward, we are no longer willing to accept, as a matter of enforcement discretion, the approach outlined in the pilot study as a means of satisfying the requirement for a valid patient-specific prescription.

In 2012 Congressional testimony, the Agency recognized that the industry has evolved to include firms such as yours that engage in large volume compounding of sterile drug products for distribution to health care facilities without patient-specific prescriptions. To facilitate the effective oversight of such firms, we believe that new legislation is needed. In the absence of such legislation, however, the Agency intends to apply its existing legal authorities.

We intend to continue inspections of your facilities to help assure your firm is meeting appropriate standards for the preparation of sterile products.

Sincerely,

/s/

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

[3] *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutory exemptions if, among other things, "the drug product is compounded for an identified individual patient based on the . . . receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . . ."); CPG at 2 ("FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.").