Analysis

The Future of Pharmacy Manufacturers

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Drug compounding has been performed for millennia but is not well understood by the general public. Compounding pharmacies have evolved on two scales: (1) traditional compounding pharmacies that are commonly associated with the mortar and pestle (Pharmacy Compounders); and (2) "non-traditional" compounding pharmacies that essentially function as manufacturers (Pharmacy Manufacturers). Over the past 15 years, regulatory oversight of Pharmacy Manufacturers has been called into question. However, clarity is now demanded due to the recent meningitis outbreak affiliated with the New England Compounding Center.[1] Although the Food and Drug Administration (FDA) cites ambiguity in the law and court decisions concerning its general and inspection authority over Pharmacy Manufacturers, oversight must be promptly addressed to avoid similar grave tragedies.

Overview of Drug Compounding

"Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient."[2] Typically, it is "used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product."[3] Additionally, compounding provides a service in response to a physician's prescription to accommodate the specialized need of a particular patient.[4] The foregoing processes are typical of Pharmacy Compounders. Compounding drugs in mass quantities, without a specific prescription, using active pharmaceutical ingredients that are not contained in FDA-approved drugs, and compounding products that are essentially copies of commercially available FDA-approved drugs, are typical of Pharmacy Manufacturers.[5] Historically, FDA leaves enforcement actions against Pharmacy Compounders to state authorities, including the applicable Board of Pharmacy, and directs its enforcement attention to Pharmacy Manufacturers.

FDA Enforcement Authority over Pharmacy Manufacturers

FDA is the agency responsible for prescription and over-the-counter drug products and the Food, Drug and Cosmetic Act of 1938 (FD&C Act)[6] governs these drugs. Due to its concern with the growth of Pharmacy Manufacturers, FDA issued compliance policy guidance in 1992 entitled "Manufacture, Distribution, and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies" (1992 CPG). FDA believed that "an increasing number of establishments with retail pharmacy licenses [were] engaging in manufacturing, distributing, and promoting unapproved new drugs for human use in a manner that [was] clearly outside the bounds of traditional pharmacy practice and that constitute[d] violations of the [FD&C Act]."[7] The 1992 CPG was FDA's early attempt to distinguish between Pharmacy Compounders and Pharmacy Manufacturers and listed nine risk areas FDA would consider to determine whether to utilize its enforcement discretion including, but not limited to, (1) promotion of specific drugs, (2) compounding drugs that were essentially copies of commercially available drugs, (3) using commercial scale manufacturing or testing equipment, (4) selling at wholesale, and (5) interstate mass production.[8]

Section 127 of the Food and Drug Administration Modernization Act of 1997 (FDAMA)[9] adopted key components of the 1992 CPG and the 1992 CPG was rescinded on January 4, 1999.[10] Of importance, FDAMA added Section 503A to the FD&C Act,[11] which outlined ways in which compounding pharmacies would be exempt from certain sections (i.e., compliance with current good manufacturing practices, adequate directions for use, and (abbreviated) new drug application process) of the FD&C Act. In essence, a compounding pharmacy may be considered a Pharmacy Manufacturer and subject to the full FD&C Act if these criteria are not met.

The current ambiguity of FDA's authority over Pharmacy Manufacturers stems from (1) litigation, which called into question the constitutionality of two provisions of Section 503A; and (2) subsequent interpretation by the courts, FDA, and legislators. At issue was Section 503A(a), which states that a valid prescription cannot be solicited from a physician by a pharmacist and Section 503A(c), which permits a pharmacy to advertise and promote that it compounds drugs so long as it does not reference "any particular drug, class of drug, or type of drug."[12]

In 2001, the Ninth Circuit in *Western States Medical Center v. Shalala* held that (1) Section 503A(a) and (c) restricted free speech and violated the First Amendment; and (2) these provisions could not be severed from the remainder of Section 503A.[13] Thus, Section 503A was held to be invalid in its entirety. On appeal in 2002, the Supreme Court in *Thompson v. Western States Medical Center* affirmed the unconstitutionality of these provisions but did not consider the severability issue.

In 2002 and in response to the *Thompson* decision, FDA issued revised compliance policy guidance entitled "Sec. 460.200, Pharmacy Compounding" (2002 CPG).[14] The 2002 CPG provided "guidance to drug compounders on how

FDA intends to address pharmacy compounding as a result of a recent decision by the Supreme Court"[15] and is specifically addressed to Pharmacy Manufacturers. FDA reiterated that it will defer to the states in matters specific to Pharmacy Compounders but will use the following criteria to determine whether to utilize its enforcement discretion over Pharmacy Manufacturers: (1) compounding drugs in anticipation of receiving prescriptions, with limited exceptions; (2) compounding drugs that were withdrawn or removed from the market for safety reasons; (3) compounding finished drugs from bulk active ingredients not components of FDA-approved drugs, with limited exceptions; (4) receiving, storing, or using drug substances without first obtaining written assurance that it was made in an FDA-registered facility; (5) receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements; (6) using commercial scale manufacturing or testing equipment; (7) compounding drugs for resale or at wholesale; (8) compounding drugs that are already commercially available or that are essentially copies of commercially available FDA-approved products, with limited exceptions; and (9) noncompliance with applicable state pharmacy laws. Failure to comply with some or all of the foregoing may result in a warning letter, seizure, injunction, and/or prosecution.

In 2008, the Fifth Circuit in *Medical Center v. Mukasey* held that the unconstitutional provisions of Section 503A(a) and (c) were severed from Section 503A and the remainder of Section 503A was still valid.[16] As the Supreme Court has not decided the severability issue, FDA may argue that the remainder of Section 503A is still good law and, at a minimum, Pharmacy Manufacturers are clearly under FDA's authority in the Fifth Circuit. As a result of *Mukasey*, FDA follows two policies related to its authority over Pharmacy Manufacturers. In the Fifth Circuit (i.e., Texas, Louisiana, Mississippi), FDA applies the "non-advertising provisions" of Section 503A to entities that are within the jurisdiction of the Fifth Circuit and to the plaintiffs that brought the case.[17] In the Ninth Circuit and elsewhere, FDA applies the enforcement policy outlined in the 2002 CPG.[18]

FDA Inspection Authority over Pharmacy Manufacturers

Pursuant to 21 U.S.C. 374(a), FDA is authorized to enter, with certain limitations, "any factory, warehouse, or establishment in which food, drugs, devices…are manufactured, processed, packed, or held, for introduction into interstate commerce…" and to inspect, with certain limitations, "such factory, warehouse, or establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein."[19] FDA also may inspect pharmacy "records, files, papers, processes, controls, and facilities" where prescription and nonprescription drugs are intended for human use, so that FDA can evaluate whether such products are adulterated or misbranded under the FD&C Act.[20] However, Pharmacy Compounders are exempt from this "heightened record inspection" (i.e., if the pharmacy complies with local pharmacy laws, regularly engages in dispensing drugs pursuant to a valid prescription and does not (and is not affiliated with any entity that) "manufacture[s], prepare[s], propagate[s], compound[s], or process[es] drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail)."[21] Subject to 21 U.S.C. 374(a)(2)(A), pharmacies that refuse FDA access to or copying of any records; and/or entry or inspection required by 21 U.S.C. 374(a),[22] may be subject to imprisonment for not more than a year, a fine of not more than $1,000, or both.[23] In certain circumstances, penalties increase up to three years imprisonment, a fine of not more than $10,000, or both.[24]

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In 2005, the Third Circuit in *Wedgewood Village Pharmacy, Inc. v. United States*, held that pharmacies are not exempt from general inspection under the FD&C Act and agreed that FDA is not required to obtain a warrant for an administrative inspection of a pharmacy.[25] But the court did find that, subject to 21 U.S.C. 374(a)(2)(A), Pharmacy Compounders are exempt from "heightened record inspection."[26]

In 2011 and on remand of *Mukasey*, the Fifth Circuit in *Medical Center Pharmacy v. Holder*, held that FDA cannot argue it has the statutory authority for "heightened record inspection."[27] Specifically, by failing to raise the issue in the first appeal, FDA waived its right to reopen its argument that

"notwithstanding [21 U.S.C. 374(a)(2)(A)], the FDA may conduct limited inspections of pharmacy records to determine if pharmacy-compounded drugs comply with the conditions set forth in §§353a and 360b(a)."[28] Accordingly, FDA does not have the authority to inspect pharmacy "records, files, papers, processes, controls, and facilities"[29] absent a pharmacy's noncompliance with 21 U.S.C. 374(a)(2)(A) (i.e., in other words, absent any evidence that the pharmacy is a Pharmacy Manufacturer).

Based on the foregoing, FDA has several options to conduct inspections of Pharmacy Manufacturers. First, FDA has general inspection authority over any pharmacy and may inspect corresponding records and files upon probable cause that a compounding pharmacy is actually a Pharmacy Manufacturer (e.g., FDA need only show that the factors outlined in the 2002 CPG for determining compounding are a reasonable basis upon which to initiate an inspection under the [FD&C Act][30]). However, it typically takes a review of records, files, and papers to establish that a Pharmacy Manufacturer is (dis)guised as a compounding pharmacy. Second, although FDA does not require a warrant to conduct an inspection, it may obtain one. Pharmacy Manufacturers may push back against FDA's authority to conduct an inspection and its enforcement authority over compounding pharmacies in general. Proactively obtaining a warrant may assist FDA in combating any such pushback. Third, FDA may coordinate an inspection with state Boards of Pharmacy, which typically have the right to inspect pharmacies in their jurisdiction.

What Now? Fundamental Principles and Proposed Resolutions

On December 19, 2012, FDA held consecutive meetings with representatives from all 50 states (including Boards of Pharmacy) and the general public to discuss a "Framework for Pharmacy Compounding: State and Federal Roles."[31] FDA also has solicited comments on several issues related to this topic.[32] The meetings focused on establishing parameters for state oversight of Pharmacy Compounders and federal oversight of Pharmacy Manufacturers, which would be subject to the FD&C Act.

Based on the FDA meetings and recent developments involving Pharmacy Manufacturers, it is evident that three fundamental principles are needed for heightened oversight of Pharmacy Manufacturers:

Principle # 1: Clear definition that distinguishes when a Pharmacy Compounder becomes a Pharmacy Manufacturer. Specifically, establish a definition of Pharmacy Manufacturers using a combination of the "non-advertising provisions" of Section 503A and the nine 2002 CPG criteria used by FDA to determine whether to utilize its enforcement discretion over Pharmacy Manufacturers.

Principle #2: Implementing regulations that (re)establish FDA's authority over Pharmacy Manufacturers. 21 USC 371(a) provides FDA general authority to promulgate regulations for the efficient enforcement of the FD&C Act. Such regulations should, at a minimum (1) clarify that FDA has enforcement authority over Pharmacy Manufacturers; (2) specify that FDA has authority to inspect pharmacies but may delegate enforcement and/or inspection of Pharmacy Compounders to the state (e.g., Boards of Pharmacy); (3) reinforce that FDA does not need a warrant for general administrative inspections of pharmacies; (4) identify if and when FDA requires a warrant to inspect pharmacy records, files, and papers; and (5) advise Pharmacy Manufacturers that they are subject to the full FD&C Act.

Principle #3: Effective lines of communication between FDA and state authorities. A national database is needed to house FDA and state information regarding inspections, enforcement actions, and other sanctions taken against Pharmacy Manufacturers. This database also should capture reports of (serious) adverse events. Transparent communication between FDA and the states, and between state Boards of Pharmacy, will mitigate and discourage the (dis)guise of Pharmacy Manufacturers.

Increased or reinforced FDA authority over Pharmacy Manufacturers would curtail the (dis)guise of Pharmacy Manufacturers, protect the health of individuals, and ultimately reduce the cost of healthcare.

Conclusion

The advent of Pharmacy Manufacturers has grown over the past 15 years, but the law has become unclear. There is current debate whether FDA or the states have inspection and enforcement authority over Pharmacy Manufacturers (i.e., applicable laws and court decisions are either ambiguous or conflict on this topic). Without clarity, public health is at heightened risk as evidenced by the recent multistate meningitis outbreak. Increased or reinforced FDA authority over Pharmacy Manufacturers would curtail the (dis)guise of Pharmacy Manufacturers, protect the health of individuals, and ultimately reduce the cost of healthcare.

About the Author

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Endnotes

1 *See* FDA updates on Multistate Outbreak of Fungal Meningitis and Other Infections, *available at* www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm (last accessed Jan. 7, 2013); *see also* Centers for Disease Control and Prevention updates on Multistate Fungal Meningitis Outbreak Investigation, *available at* www.cdc.gov/hai/outbreaks/meningitis.html (last accessed Jan. 7, 2013).

2 *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360–61 (2002).

3 *Id.* at 361.

4 Response From the Food and Drug Administration to Letter From Sen. Grassley on Compounding of Inhalation Drugs (Oct. 2, 2006), *available at* www.finance.senate.gov/newsroom/chairman/release/?id=df2a76ac-2f16-4c4b-9d68-cbf58754ae30 (last accessed Jan. 7, 2013).

5 *See* FDA Pharmacy Compounding Warning Letters, *available at* www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm (last accessed Jan. 7, 2013).

6 21 U.S.C. §§ 301-399 (2012).

7 *Thompson, supra* note 2, 535 U.S. at 362–63.

8 *Id.* at 363.

9 21 U.S.C. § 353a.

10 64 Fed. Reg. 1207, 1208 (announcing the rescission of Compliance Policy Guide section 460.200, formerly numbered as 7132.16).

11 21 U.S.C. § 353a.

12 21 U.S.C. § 353a(c).

13 *Western States Medical Center v. Shalala*, 238 F.3d 1090, 97 (9th Cir. 2001).

14 Food and Drug Administration Compliance Policy Guide Section 460.200 (May 29, 2002), *available at* www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm (last accessed Jan. 7, 2013).

15 67 Fed. Reg. 39409 (announcing the availability of guidance for FDA staff and industry entitled Sec. 460.200 Pharmacy Compounding).

16 *Medical Center Pharmacy et al., v. Mukasey*, 536 F.3d 383, 409 (5th Cir. 2008).

17 Warning Letter to Steven's Pharmacy (Nov. 12, 2008), *available at* www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048074.htm; Warning Letter to Civic Center Pharmacy (Dec. 16, 2008), *available at* www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048048.htm (last accessed Jan. 7, 2013).

18 *Id.*

19 21 U.S.C. § 374(a)(1).

20 *Id.*

21 21 U.S.C. § 374(a)(2)(A).

22 21 U.S.C. §§ 331(e), (f).

23 21 U.S.C. § 333(a).

24 *Id.*

25 *Wedgewood Village Pharmacy, Inc., v. United States*, 421 F.3d 263, 275 (2005).

26 *Id.* at 271.

27 *Medical Center Pharmacy v. Holder*, 634 F.3d 830, 836 (5th Cir. 2011).

28 *Id.* at 832.

29 21 U.S.C. § 374(a)(1).

30 *Wedgewood, supra* note 25, 421 F.3d. at 272-273.

31 77 Fed. Reg. 71009.

32 *Id.*