



# Federal Authority to Regulate the Compounding of Human Drugs

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## Summary

In light of the 2012 fungal meningitis outbreak, believed to have been caused by a contaminated compounded steroid injection, the regulation of human drug compounding has received significant attention. Drug compounding in its traditional form is the process of combining, mixing, or altering ingredients in order to create a medication for a particular patient. However, as illustrated by the entity that created the steroid medication linked with the meningitis outbreak, concerns have been raised about compounding pharmacies producing drugs on a larger scale. While drug compounding has historically been the focus of state governments through their regulation of pharmacies, questions have arisen regarding the extent the federal government can regulate the practice of compounding through the Food, Drug, and Cosmetic Act (FDCA).

Federal authority over compounding largely stems from the FDCA, enacted in 1938, and its subsequent amendments, including the Food and Drug Administration Modernization Act (FDAMA) of 1997, which added compounding specific provisions to the FDCA in section 503A. A First Amendment challenge to section 503A's advertising provisions and a resulting Supreme Court decision has created a split amongst the federal courts regarding whether section 503A has any legal effect. The legal uncertainty regarding section 503A, coupled with section 503A's basis in the FDCA's "new drug," "adulteration," and "misbranding" provisions leads to an examination of the scope of federal authority under the base statute. Courts appear to agree that the federal government can regulate compounding activity that is akin to manufacturing, and courts have afforded deference to the FDA's interpretation of when a compounder is acting like a manufacturer. However, uncertainty remains regarding the possible limits to the FDA's power to regulate traditional compounding activities. This report will examine the FDA's regulation of drug compounding and will discuss relevant legal authorities. The report will conclude by discussing potential limits to the FDA's authority to regulate human drug compounding.

## Contents

Background.....	1
Federal Regulation of Compounded Drugs .....	2
Compounding Before the 1938 Food, Drug, and Cosmetic Act.....	2
The 1938 Food, Drug, and Cosmetic Act .....	2
Kefauver-Harris Drug Amendments of 1962 .....	5
Food and Drug Administration Modernization Act of 1997 and Compounding .....	5
FDAMA and Federal Authority After <i>Thompson v. Western States Medical Center</i> .....	6
Limits on Federal Authority to Regulate Compounded Drugs .....	9

## Tables

Table 1. Factors Guiding Whether the FDA Will Take Action Against a Compounder of Human Drugs.....	8
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## Contacts

Author Contact Information.....	13
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## Background

Drug compounding traditionally refers to the process in which a pharmacist combines, mixes, or alters various ingredients to create a medication that is “tailored to the needs” of an individual patient.<sup>1</sup> Compounding is generally used to prepare medications that are not commercially available, such as a drug in a lower dosage for a child, or a drug without a dye or a preservative in response to a patient allergy.<sup>2</sup>

Recent events have refocused attentions on compounding and the federal role in regulating drug compounding. In the fall of 2012, the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) identified the presence of bacterial and/or fungal contamination in steroid injections from a New England compounding pharmacy.<sup>3</sup> The contamination has been linked with a multistate fungal meningitis outbreak that resulted in over 50 deaths.<sup>4</sup>

As a consequence, questions have arisen regarding the safety of compounded drugs and the role of federal and state governments in regulating compounded drugs and compounding pharmacies. Congressional hearings held by the Energy and Commerce Committee of the U.S. House of Representatives and the Health, Education, Labor, and Pensions Committee of the U.S. Senate probed the current policy and legal questions prompted by the meningitis outbreak.<sup>5</sup> One of the issues raised at these hearings was the extent of federal authority over compounding.<sup>6</sup> During these hearings, the Commissioner of the FDA noted the need for clarification and strengthening of the FDA’s authority to “prevent” contaminations caused by compounding from occurring in the future,<sup>7</sup> while other representatives of professional associations contended that existing FDA authorities were adequate to have prevented the 2012 outbreak.<sup>8</sup> Thus, in the wake of the 2012

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<sup>1</sup> See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360-61 (2002).

<sup>2</sup> *Id.* at 361.

<sup>3</sup> Centers for Disease Control and Prevention, *Multistate Fungal Meningitis Outbreak Investigation—Current Case Count*, <http://www.cdc.gov/hai/outbreaks/meningitis.html>.

<sup>4</sup> Centers for Disease Control and Prevention, *Multistate Fungal Meningitis Outbreak Investigation—Current Case Count*, <http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html> (noting that as of March 25, 2013, 730 cases of fungal infections had been linked to steroid injections, resulting in 51 deaths).

<sup>5</sup> See U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, *The Fungal Meningitis Outbreak: Could It Have Been Prevented*, 112<sup>th</sup> Cong., 2<sup>nd</sup> sess., November 14, 2012; see also U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak*, 112<sup>th</sup> Cong., 2<sup>nd</sup> sess., November 15, 2012, <http://www.help.senate.gov/hearings/hearing/?id=5f5def0d-5056-a032-5297-eab57634d209>.

<sup>6</sup> U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak*, 112<sup>th</sup> Cong., 2<sup>nd</sup> sess., November 15, 2012, <http://www.help.senate.gov/hearings/hearing/?id=5f5def0d-5056-a032-5297-eab57634d209>.

<sup>7</sup> See Margaret A. Hamburg, Testimony before U.S. Congress, Senate Health, Education, Labor and Pensions Committee, *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak*, 113<sup>th</sup> Cong., November 15, 2012, <http://www.help.senate.gov/imo/media/doc/Hamburg3.pdf> (“As described above, FDA’s ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by gaps and ambiguities in the law, which have led to legal challenges to FDA’s authority to inspect pharmacies and take appropriate enforcement actions.”)

<sup>8</sup> See, e.g., David Miller, International Academy of Compounding Pharmacists, Testimony before U.S. Congress, Senate Health, Education, Labor and Pensions Committee, *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak*, 113<sup>th</sup> Cong., November 15, 2012, <http://www.help.senate.gov/imo/media/doc/Miller8.pdf> (“From (continued...)”).

meningitis outbreak, a central issue that this report explores is the nature and scope of federal authority to regulate entities that compound drugs for humans.

## **Federal Regulation of Compounded Drugs**

### **Compounding Before the 1938 Food, Drug, and Cosmetic Act**

At the inception of the modern federal drug law, compounding was practiced extensively and widely regulated by the states.<sup>9</sup> On June 30, 1906, Congress enacted the Pure Food and Drug Act,<sup>10</sup> the first significant drug legislation that attempted to address the problems of drug safety and effectiveness. However, the Pure Food and Drug Act, which was passed with the purpose to “secure the purity of food and drugs and to inform purchasers of what they are buying,”<sup>11</sup> did not mandate a federal premarket approval or notification system for new drugs, let alone attempt to substantively regulate drug compounding. Instead, the 1906 act was concerned with false labeling of food and drugs, and as long as a drug compounder made no false or misleading claims with regard to the ingredients in a product, the compounder’s actions would not run afoul of the Pure Food and Drug Act.<sup>12</sup> The advent of modern federal regulation of drugs arrived 22 years later when Congress enacted the Food, Drug, and Cosmetic Act (FDCA).<sup>13</sup>

### **The 1938 Food, Drug, and Cosmetic Act**

The Food, Drug, and Cosmetic Act of 1938 established a complex and comprehensive scheme for regulating drugs that are distributed in interstate commerce.<sup>14</sup> While the 1938 act on its face is silent with respect to compounding,<sup>15</sup> three provisions are particularly relevant to the subject. First, the act defines a “new drug” as “[a]ny drug ... not generally recognized ... as safe ... for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”<sup>16</sup> The statute forbids introducing any “new drug” into interstate commerce without FDA approval.<sup>17</sup> Under current law, to obtain FDA approval, the sponsor must submit an extensive application to

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(...continued)

the federal standpoint, the FDCA’s existing inspection provision, section 704, allows FDA oversight when a pharmacy is not operating in conformity with governing state laws, or akin to a drug manufacturer.”)

<sup>9</sup> See *Joint Session of Am. Pharm. Ass’n, et al.*, 17 J. Am. Pharm. Ass’n 1000, 1010-13 (1938).

<sup>10</sup> P.L. 59-384, 34 Stat. 768 (1906).

<sup>11</sup> *United States v. Antikamnia Chem. Co.*, 231 U.S. 654, 665 (1913)

<sup>12</sup> See James Harvey Young, *The Toadstool Millionaires: A Social History of Patent Medicines in America Before Federal Regulation* 9, 243-44 (Princeton Univ. Press. 1961).

<sup>13</sup> P.L.75-717, 52 Stat. 1057 (1938).

<sup>14</sup> See generally CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Susan Thaul.

<sup>15</sup> *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209, 1254 n.7 (M.D. Fl. 2011) (noting that the FDCA is “silent on the topic” of compounding).

<sup>16</sup> 21 U.S.C. § 321(p)(1). The “new drug” provision of the FDCA contains a “grandfather clause” that excludes drugs subject to regulation under a 1906 federal statute, if the labeling is appropriate. *Id.* The FDCA broadly defines the term “drug” to include “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals.” 21 U.S.C. § 321(g)(1)(B).

<sup>17</sup> 21 U.S.C. §§ 331(d), 355(a).

the FDA containing data that demonstrate that the new drug is both safe and effective for its intended uses in humans and that it will be manufactured such that the drug will preserve its identity, strength, quality, and purity.<sup>18</sup>

In addition to the act's "new drug" provisions, the current version of the FDCA has "adulteration" provisions that deem a drug to be "adulterated" if, among other things, the drug and the methods used in its creation do not conform with "current good manufacturing practices" that ensure the product's safety and quality.<sup>19</sup> The FDA has promulgated regulations that describe current good manufacturing practices.<sup>20</sup> Those regulations include, for example, requirements that the equipment used in the manufacturing of drugs be cleaned or sterilized at certain times<sup>21</sup> and that records related to manufacturing practices be maintained for at least a year after the expiration date of a batch of drugs.<sup>22</sup>

Third, the 1938 act contains provisions that discuss when a drug is "misbranded."<sup>23</sup> In relevant part, a drug can be "misbranded" if the drug's labeling<sup>24</sup> fails to bear "adequate directions for use."<sup>25</sup> FDA regulations generally define "adequate directions for use" as directions under which a layperson can use a drug "safely and for which it is intended."<sup>26</sup> Federal regulations further note several examples of when a direction may be "inadequate," such as the omission of "all" purposes for which the drug is intended<sup>27</sup> or the incorrect specification of the time of administration of a drug.<sup>28</sup>

Section 301 of the FDCA prohibits an individual from introducing or delivering into interstate commerce (1) a "new drug" without prior FDA approval,<sup>29</sup> (2) an "adulterated" drug,<sup>30</sup> or (3) a

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<sup>18</sup> 21 U.S.C. §§ 355(a)-(d). The FDCA has specific provisions that discuss the role of new animal drugs. Specifically, "new animal drugs" that have not been approved by the FDA are "unsafe" and "adulterated." See 21 U.S.C. §§ 351(a)(5) & 360b(a)(1)(A).

<sup>19</sup> 21 U.S.C. § 351(a)(1)(B). The precursor to the modern language regarding "good manufacturing practices" in the 1938 Act were provisions that broadly deemed a drug to be "adulterated" if it had been "prepared, packed, or held under insanitary conditions ..." See P.L.75-717, § 501(a)(2). The provision on "good manufacturing practices" resulted from the Kefauver-Harris Drug Amendments of 1962. See *infra*.

<sup>20</sup> See 21 C.F.R. parts 210, 211, 225, and 226.

<sup>21</sup> See 21 C.F.R. § 211.67.

<sup>22</sup> See 21 C.F.R. § 211.180.

<sup>23</sup> See 21 U.S.C. § 352.

<sup>24</sup> Labeling is defined under the FDCA to include "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The Supreme Court, in *Kordel v. United States*, broadly interpreted the phrase "accompanying such article" to include materials that supplement or explain the product. 335 U.S. 345, 349 (1948).

<sup>25</sup> 21 U.S.C. § 352(f)(1). The statute does allow the Secretary to promulgate regulations exempting a drug if providing "adequate directions for use" are not necessary for the "protection of public health." *Id.* 21 C.F.R. § 201.122 exempts from the FDCA's "adequate directions for use" requirement drugs in bulk form intended for processing, repackaging or use in the "manufacture of another drug" if the bulk drug contains labeling that indicates its proper use. *Id.* However, the exemption only extends to a drug where an approved new drug application or new animal drug application or new animal drug index listing is affiliated with the production. See 21 C.F.R. 201.122(a)-(c).

<sup>26</sup> 21 C.F.R. § 201.5.

<sup>27</sup> 21 C.F.R. § 201.5(a).

<sup>28</sup> 21 C.F.R. § 201.5(e). For example, a drug label could be inadequate if it incorrectly specifies that the drug should be taken with food. *Id.*

<sup>29</sup> 21 U.S.C. § 301(d).

<sup>30</sup> 21 U.S.C. § 301(a).

“misbranded” drug.<sup>31</sup> That same section also prohibits the “adulteration” or “misbranding” of a drug in interstate commerce,<sup>32</sup> the “receipt in interstate commerce of” an adulterated or misbranded drug, and the manufacturing of any adulterated or misbranded drugs.<sup>33</sup> The FDCA authorizes the United States to seek injunctive relief in federal court to restrain any violations of section 301,<sup>34</sup> and the law subjects individuals who have violated the FDCA’s prohibitions to civil fines and criminal penalties.<sup>35</sup> Furthermore, section 304 of the FDCA allows the United States to proceed against and seize mislabeled or adulterated drugs.<sup>36</sup>

The breadth of the FDCA’s “new drug,” “adulteration,” and “misbranding” provisions, on their face, have the potential to touch on local, traditional compounding efforts.<sup>37</sup> However, for nearly 50 years following the passage of the FDCA, the FDA did not use the FDCA’s “new drug,” “adulteration,” or “misbranding” provisions as a means to regulate the practice of compounding.<sup>38</sup> Instead, the “FDA generally left regulation of compounding to the States,” and “[p]harmacists continued to provide patients with compounded drugs without applying for FDA approval of those drugs.”<sup>39</sup> The rationale for the FDA’s initial approach toward drug compounding was that it is widely recognized that compounded drugs could not meet the FDCA’s “new drug” requirements.<sup>40</sup> As the Supreme Court has noted, subjecting compounding pharmacies to the statute’s approval requirements “would as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment.”<sup>41</sup> This is because FDA approval requires “proof of the safety and effectiveness of a new drug ... [as] established by rigorous, scientifically valid clinical studies,” a process that is extremely time consuming and costly.<sup>42</sup> As the Court observed, it is neither medically practicable nor “economically feasible” to subject compounded medications to the type of testing required by the FDCA for a new drug approval,<sup>43</sup> “requiring such testing would force pharmacists to stop providing compounding drugs.”<sup>44</sup>

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<sup>31</sup> 21 U.S.C. § 301(a).

<sup>32</sup> 21 U.S.C. § 301(b).

<sup>33</sup> 21 U.S.C. § 301(c).

<sup>34</sup> 21 U.S.C. § 332(a).

<sup>35</sup> See 21 U.S.C. § 333.

<sup>36</sup> 21 U.S.C. § 334(a).

<sup>37</sup> See *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 395 (5<sup>th</sup> Cir. 2008) (noting the language of the FDCA’s new drug definition to be “both plain and expansive”); *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209, 1237 (M.D. Fl. 2011) (noting that the FDCA’s provision if “read literally” would apply to bulk compounding).

<sup>38</sup> See *W. States*, 535 U.S. at 362.

<sup>39</sup> *Id.*

<sup>40</sup> Statement of Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, before the Senate Committee on Health, Education, Labor and Pensions, Hearing on “Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients,” (October 23, 2003). See also *Western States*, 535 U.S. at 369 (“... it would not make sense to require compounded drugs created to meet the unique needs of patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs.”)

<sup>41</sup> *W. States*, 535 U.S. at 369.

<sup>42</sup> *Id.* at 368-69.

<sup>43</sup> 21 U.S.C. § 355.

<sup>44</sup> *W. States*, 535 U.S. at 370.



## Kefauver-Harris Drug Amendments of 1962

The Kefauver-Harris Drug Amendments of 1962 (Drug Amendments), enacted in the wake of the thalidomide crisis of the early 1960s, constituted the first mentioning of compounding in federal drug law.<sup>45</sup> In relevant part, the Drug Amendments required manufacturers and others to register their establishments and strengthened the ability of the FDA to conduct on-site inspections.<sup>46</sup> The Drug Amendments, however, exempted “pharmacies ... which do not ... compound, or process drugs for sale other than in the regular course of their business of dispensing or selling drugs at retail” from registration requirements<sup>47</sup> and from enhanced inspections of a pharmacy’s books and records.<sup>48</sup> Case law interpreting the Drug Amendments of 1962, however, has held that federal authorities have the right to enter establishments involved in the production of drugs to inspect equipment, materials, containers, and labeling used in the production process.<sup>49</sup>

## Food and Drug Administration Modernization Act of 1997 and Compounding

In 1997, Congress amended the FDCA through the Food and Drug Administration Modernization Act (FDAMA).<sup>50</sup> The amendment contained provisions on drug compounding that resulted, in part, from a growing concern that an “increasing number of establishments with retail pharmacy licenses [were] engaged in manufacturing and distributing unapproved new drugs for human use in a manner that was clearly outside the bounds of traditional pharmacy practice.”<sup>51</sup> Put another way, the FDA was concerned that “some pharmacists were manufacturing and selling drugs under the guise of compounding,” as a way of avoiding the FDCA’s “new drug,” “adulteration,” and “misbranding” provisions.<sup>52</sup> Accordingly, the intent of the FDAMA’s compounding provisions was “to clarify the application of the [FDCA] to professional practice of pharmacists’ compounding of drug products.”<sup>53</sup>

To do so, the FDAMA explicitly deems that three provisions of the FDCA are inapplicable to drug compounding that complies with various requirements.<sup>54</sup> The three provisions are the

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<sup>45</sup> P.L. 87-781, 76 Stat. 780 (1962) (current version as amended at 21 U.S.C. §§ 301-392).

<sup>46</sup> *Id.*; see generally Bryan Christopher Moody, “Prescription Medication and Consumer Protection: A Time for Reform,” *The Journal of Pharmacy & Law*, vol. 5 (1996), p. 21 (“Additionally, the Drug Amendments of 1962 required the following: that drug companies register with the FDA and be inspected by the FDA every two years, that all drug company records be made available for inspection, that adverse drug reactions be transmitted to the FDA, that the FDA be given full authority to regulate the advertising of prescription drugs and all advertising must relate to the adverse effects and contraindications to consumer, and that investigational drug studies require informed patient consent prior to trials on humans.”)

<sup>47</sup> See 21 U.S.C. § 360(g)(1).

<sup>48</sup> See 21 U.S.C. § 374(a)(2)(A).

<sup>49</sup> See *Wedgewood Vill. Pharm., Inc. v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) (holding that a compounder was not exempt from non-record inspections under 21 U.S.C. § 374(a)).

<sup>50</sup> P.L. 105-115, 111 Stat. 2296 (1997). The FDAMA was a product of a 1992 FDA Compliance Policy Guide that outlined the agency’s policies regarding drug compounding. See *W. States.*, 535 U.S. at 362-64 (“Congress turned portions of this policy into law when it enacted the FDAMA in 1997).

<sup>51</sup> CPG § 7132.16 (Mar. 1992).

<sup>52</sup> *W. States.*, 535 U.S. at 362.

<sup>53</sup> S.Rept. 105-43, Committee on Labor and Human Resources, p. 67 (July 1, 1997).

<sup>54</sup> See 21 U.S.C. § 353a(a).



FDCA's provisions on (1) the sale of a "new drug," (2) adulteration and the need to adhere to "good manufacturing practices," and (3) misbranding and the need to provide "adequate directions for use" on a drug.<sup>55</sup> With respect to requirements for compounding, the law requires that compounding be done by a licensed pharmacist or physician in response to a valid prescription for an identified individual patient, or, if prepared before the receipt of such a prescription, the drug be made in only "limited quantities" and in response to a history of the licensed pharmacist's or physician's receipt of valid prescription orders for that drug product within an established relationship between the pharmacist, the patient, and the prescriber.<sup>56</sup> Additionally, the law requires that the compounded drug be made from approved ingredients that meet certain standards, and the compounded drug may not appear on an FDA list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or ineffective.<sup>57</sup> The FDAMA also prohibits the compounding of drugs in "inordinate amounts" such that the drugs are "essentially copies of a commercially available drug product."<sup>58</sup> The law also allows the FDA to identify certain drug products that present "demonstrable difficulties" for compounding in terms of safety or effectiveness, prohibiting the compounding of such articles.<sup>59</sup> In states that have not entered into an agreement with the FDA addressing the distribution of "inordinate amounts" of compounded drugs in interstate commerce, the pharmacy, pharmacist, or physician compounding the drug may not distribute compounded drugs out of state in quantities exceeding 5% of that entity's total prescription orders.<sup>60</sup>

## FDAMA and Federal Authority After *Thompson v. Western States Medical Center*

The FDAMA also included a ban on advertising by compounders.<sup>61</sup> However, in 2003, the Supreme Court in *Thompson v. Western States Medical Center* invalidated the FDAMA's advertising provisions on First Amendment grounds.<sup>62</sup> Generally, if a part of a law is held to be unconstitutional, the unconstitutional provision is "severable" or "dropped" from what remains of a law unless it is "evident that the Legislature would not have enacted" the remaining provisions independently of the unconstitutional provision.<sup>63</sup> In the wake of *Western States*, a split has emerged amongst the federal circuit court of appeals about whether the remaining provisions of the FDAMA are "severable" from the advertising provision at issue in the *Western States* case.<sup>64</sup>

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<sup>55</sup> *Id.* (citing sections 501(a)(2)(B) (adulteration), 502(f)(1) (misbranding), 505 (new drugs)).

<sup>56</sup> 21 U.S.C. § 353a(a).

<sup>57</sup> 21 U.S.C. §§ 353a(b)(1)(A)-(C).

<sup>58</sup> 21 U.S.C. § 353a(b)(1)(D). The definition of the term "inordinate amounts" is delegated in the statute to the Secretary of Health and Human Services. *Id.* FDA regulations have not yet formally defined the term "inordinate amounts." See 21 C.F.R. § 216.23 *et seq.*

<sup>59</sup> 21 U.S.C. § 353a(b)(3)(A).

<sup>60</sup> 21 U.S.C. § 353a(b)(3)(B).

<sup>61</sup> 21 U.S.C. § 353a(c).

<sup>62</sup> 535 U.S. at 360.

<sup>63</sup> See *Alaska Airlines, Inc. v. Brock*, 480 U.S. 678, 684 (1987) (internal quotations and citations omitted).

<sup>64</sup> Compare *W. State Med Ctr. v. Shalala*, 238 F.3d 1090, 1096-98 (9<sup>th</sup> Cir. 2001), *aff'd on other grounds*, 535 U.S. 357 (2002), with *Medical Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 401 (5<sup>th</sup> Cir. 2008). The Supreme Court in *Western States* declined to rule on the issue of severability. 535 U.S. at 366 ("Because neither party petitioned for certiorari on the severability issue, we have no occasion to review that portion of the Court of Appeals decision.") For a more in depth discussion on these two cases and the resulting circuit split, see CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

As a consequence, within the states within the Ninth Circuit,<sup>65</sup> the controlling precedent renders the remaining provisions of the FDAMA inoperable.<sup>66</sup> The opposite is true in the Fifth Circuit,<sup>67</sup> and the legal effect of the FDAMA is unresolved in the rest of the country.<sup>68</sup> The FDA noted in 2002, prior to the Fifth Circuit's decision, that in light of the Supreme Court decision, the FDAMA "is now invalid,"<sup>69</sup> and instead, the FDA "outlined the criteria"<sup>70</sup> it would use to assess "what types of compounding might be subject to enforcement under current law" (i.e., the FDCA)<sup>71</sup> in a 2002 Compliance Policy Guide (CPG).<sup>72</sup> In the wake of the Fifth Circuit's decision, the FDA has taken the position<sup>73</sup> that the agency "will apply the non-advertising provisions of section 503A to entities covered by this provision that are located within the jurisdiction of the Fifth Circuit ... as well as to the plaintiffs that brought the *Medical Center* case."<sup>74</sup>

The 2002 CPG was issued out of a "need for immediate guidance" for "the compounding industry on what factors the [FDA] will consider in exercising its enforcement discretion regarding pharmacy compounding."<sup>75</sup> The policy guidance generally notes while the FDA "will continue to defer to state authorities regarding less significant violations of the [FDCA] related to pharmacy

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<sup>65</sup> The Ninth Circuit Court of Appeals covers the states of Alaska, Arizona, California, Idaho, Montana, Nevada, Oregon, Washington, and Hawaii. See 28 U.S.C. § 41.

<sup>66</sup> *W. State Med Ctr.*, 238 F.3d at 1096-98.

<sup>67</sup> *Medical Ctr. Pharmacy*, 536 F.3d at 401. The Fifth Circuit's jurisdiction is limited to the states of Louisiana, Mississippi, and Texas. See 28 U.S.C. § 41.

<sup>68</sup> An unpublished federal district court decision in Colorado, faced with both parties in agreement that the FDAMA's advertising provisions were severable from the rest of the act, opined that the Fifth Circuit's decision with respect to severability was not "so palpably incorrect that applying its rule would be clearly be error." See *United States v. Bader*, No. 07-CR-338, 2009 WL 2219258 at \*9 (D. Colo. July 23, 2009), *aff'd* 678 F.3d 858 (11<sup>th</sup> Cir. 2012). On appeal to the Tenth Circuit, the appellate court found the Fifth Circuit's decision to be inapplicable to the case at hand as the case did not implicate any provisions of the FDAMA. 678 F.3d at 888-89 ("Consequently, *Medical Center Pharmacy* is inapposite.")

<sup>69</sup> Compliance Policy Guide § 460.200 (May 29, 2002).

<sup>70</sup> *Wedgewood Vill. Pharm., Inc. v. United States*, 421 F.3d 263, 272 (3d Cir. 2005).

<sup>71</sup> *Bader*, 678 F.3d at 888 (noting that the "overarching premise of [the 2002 CPG on compounding] was that, generally, the FDA had maintained some degree of regulatory authority over pharmacy compounding both before *Western States* ... and the FDAMA").

<sup>72</sup> CPG § 460.200 (May 29, 2002); see generally *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1263 (S.D. Fla. 2005) (noting that "in the wake of *Western States*, the FDA issued a new [CPG] dealing with compounded drugs [similar to the one codified in the FDAMA] ... [t]his new policy is unaffected by the decision in *Western States*).

<sup>73</sup> See Food and Drug Administration, "Medical Center Pharmacy v. Mukasey," press release, May 6, 2009, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm134919.htm> ("In the meantime, FDA will follow the court's decision in the Fifth Circuit and with respect to the plaintiffs covered by the decision. Elsewhere, the agency will continue to follow the enforcement approach reflected in the Compliance Policy Guide (CPG) section 460.200 [Pharmacy Compounding] issued by FDA on May 29, 2002."); see also Letter from Alonza E. Cruse, Director, Los Angeles District, U.S. Food and Drug Administration, to Ari S. Schafer, Civic Center Pharmacy (December 16, 2008), available at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048048.htm>; see also Letter from Alonza E. Cruse, Director, Los Angeles District, U.S. Food and Drug Administration, to Charles T. Bonner, Steven's Pharmacy (November 12, 2008), available at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048074.htm>.

<sup>74</sup> The practical effect of whether the FDAMA's compounding provisions apply or whether the CPG applies is not readily apparent, as both the compounding provisions of the FDAMA and the CPG are rooted in authority provided by the FDCA. Compare 21 U.S.C. § 503A(a) (stating that sections 501(a)(2)(B), 502(f)(1) and 505 of the FDCA do not apply to certain compounding activity) with CPG § 460.200 (May 29, 2002) (providing guidance on "what types of compounding might be subject to enforcement action under current law).

<sup>75</sup> CPG § 460.200 (May 29, 2002).

compounding of human drugs,<sup>76</sup> the agency will focus on “concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act.”<sup>77</sup> In determining whether to take an enforcement action against a compounding entity, the CPG notes nine non-exhaustive factors that will guide regulators.<sup>78</sup> The factors are summarized in **Table 1**.<sup>79</sup>

**Table 1. Factors Guiding Whether the FDA Will Take Action Against a Compounder of Human Drugs**

Is the compounding ... ?	If yes, is the FDA more likely to assert its regulatory authority?
... done in anticipation of receiving prescriptions?	No
... involving a drug that was withdrawn or removed from the market for safety reasons? <sup>a</sup>	Yes
... based from bulk active ingredients?	Yes (if not from a FDA-approved drug or without a FDA sanctioned New Drug Application)
... done without obtaining written assurance from the supplier that the drug substances were made in an FDA-registered facility?	Yes
... not in compliance with official compendia requirements?	Yes
... using commercial scale manufacturing or testing equipment?	Yes
... done for third parties who will resell the drugs?	Yes
... of drug products that are commercially available in the marketplace or essentially copies of commercially available drugs?	Yes
... failing to comply with applicable state law?	Yes

**Source:** Prepared by CRS

**Notes:** Derived from FDA Compliance Policy Guide § 460.200 (May 29, 2002).

- a. See 21 C.F.R. § 216.24 (list of drug products withdrawn or removed from the market for reasons of safety or effectiveness).

In 2003, the FDA issued guidance with regard to veterinary compounding.<sup>80</sup> Similar to its 2002 guidance on human compounding, the FDA noted its concerns regarding compounding that is “clearly outside of the bounds of traditional pharmacy practice” and is “intended to circumvent [the FDCA’s] drug approval process and provide for the mass marketing of products that have been produced with little to no quality control or manufacturing standards to ensure the purity, potency, and stability of the product.”<sup>81</sup> The 2003 CPG announced that while the FDA will “generally” “defer to state authorities regarding the day-to-day regulation of compounding by

<sup>76</sup> *Id.*

<sup>77</sup> *Id.*

<sup>78</sup> *Id.*

<sup>79</sup> For a more in depth discussion on the 2002 FDA CPG on compounding, see CRS Report R40503, *FDA’s Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

<sup>80</sup> See CPG § 608.400 (July 14, 2003). The FDAMA’s provision on compounding addressed human, not animal, use. See 21 U.S.C. § 353a(a).

<sup>81</sup> See CPG § 608.400 (July 14, 2003).

veterinarians,” federal authority will be asserted when the activities in question raise the “kinds of concerns normally associated with a drug manufacturer” and “result in significant violations of the new animal drug, adulteration, or misbranding provisions” of the act.<sup>82</sup> In determining whether to take an enforcement action against a compounding entity, the CPG on animal drug compounding notes 13 non-exhaustive factors that will guide regulators.<sup>83</sup> The factors largely mirror the concerns illustrated in the 2002 CPG for human drug compounding and include concerns common to both human and animal drug compounding.<sup>84</sup> For example, the FDA noted that the volume of drugs being compounded or whether the compounding used commercial scale manufacturing equipment would be used by federal officials when determining whether to take an enforcement action against an animal drug compounder.<sup>85</sup>

Both the 2002 and 2003 CPGs on drug compounding make clear that the FDA, as a matter of public policy, will focus its enforcement efforts on compounding efforts that are akin to “manufacturing” and will defer to state governments with respect to “traditional compounding.”<sup>86</sup> As a matter of law, the FDA does not attempt, in the two CPGs, to limit its authority under the FDCA. Instead, the CPGs note that the FDCA does not “distinguish compounding from manufacturing”<sup>87</sup> and deem violations of the FDCA that do not relate to manufacturing to be a concern of “state authorities.”<sup>88</sup>

## Limits on Federal Authority to Regulate Compounded Drugs

The legal uncertainty about the validity of the compounding provisions of the FDAMA, coupled with the FDA’s renewed reliance on the FDCA’s new drug, adulteration, and misbranding provisions as the source of the federal authority to regulate drug compounding, has prompted considerable discussion with respect to the extent of the FDA’s authority under the 1938 act. Moreover, even if the FDAMA’s compounding provisions still have legal effect, the provisions are based on blanket exemptions for certain compounding activity from the FDCA’s new drug,

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<sup>82</sup> *Id.* The “new animal drug” provisions of the FDCA are similar, but not identical, to the provisions for human drugs. Pursuant to section 512 of the FDCA, absent FDA approval, a “new animal drug” is “deemed unsafe, which, in turn, renders the drug “adulterated” under section 501(a) and “misbranded” under section 502(f) unless the drug bears “adequate directions for use.” See 21 U.S.C. § 360b. Hence, similar “to human drugs, any drug ... the composition of which has not already been approved by the FDA constitutes a ‘new animal drug’ within the meaning of the statute.” See *Medical Ctr. Pharm.*, 536 F.3d at 407 (internal citations omitted).

<sup>83</sup> See CPG § 460.200 (May 29, 2002); see also CPG § 608.400 (July 14, 2003).

<sup>84</sup> *Id.*

<sup>85</sup> *Id.* While animal drug compounding is beyond the scope of this report, the overlap in the legal framework for human and animal drugs, see *supra* footnote 82, make the FDA’s 2003 guidance useful to gauge the agency’s general approach toward the regulation of drug compounding.

<sup>86</sup> *Id.*

<sup>87</sup> *Id.*

<sup>88</sup> See CPG § 460.200 (May 29, 2002). The CPG, as a general policy statement, as opposed to a rule that affords the public notice and an opportunity to comment on the rule, does not have the force of law,<sup>88</sup> and does not receive the fullest deference from courts of law. See *United States v. Mead Corp.*, 533 U.S. 218, 229 (2001). Instead, a CPG “merely provide[s] guidance for FDA agents in determining possible violations, within their discretion.” *Professionals & Patients for Customized Care v. Shalala*, 847 F. Supp. 1359, 1365 (S.D. Tex. 1994). For a lengthier discussion of the legal effect of the CPG, see CRS Report R40503, *FDA’s Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

adulteration, and misbranding requirements, all of which are based on the assumption that broad federal authority to regulate drug compounding exists.<sup>89</sup> With this backdrop, a debate has arisen regarding the limits of federal authority under the FDCA with respect to the regulation of drug compounding.

The FDA maintains the position that pharmacy-compounded drugs are “new drugs” or “new animal drugs” within the meaning of the FDCA,<sup>90</sup> and, therefore, the entire practice of compounding is “under FDA scrutiny.”<sup>91</sup> According to the agency, as a “matter of discretion” the FDA has “historically declined” to take “enforcement action against pharmacies engaged in traditional drug compounding.”<sup>92</sup> Pharmacists, in response, have disputed the reach of the FDA’s authority, finding “cold comfort in the FDA’s promised self-restraint.”<sup>93</sup> Instead, those who oppose the FDA’s theory of its authority to regulate compounding contend that the practice of compounding was widespread at the time of the 1938 act, and Congress would not have intended to expand the FDA’s regulatory authority to make compounding activities covered by the act’s new drug, adulteration, and misbranding provisions,<sup>94</sup> regulations that, if enforced literally, would functionally prohibit traditional compounding.<sup>95</sup>

Courts that have examined the issue have all agreed that the FDA has *some* authority to regulate compounding.<sup>96</sup> Specifically, case law appears to find that the FDCA does provide the federal government with the authority to prohibit pharmacists from manufacturing under the guise of compounding.<sup>97</sup> According to one recent court decision, “[t]o the extent that a pharmacist’s bulk compounding activity moves beyond the bound of traditional compounding and begins to approximate the ‘manufacturing’ of unapproved drugs, there seems little question that this activity is squarely within the crosshairs of the FDCA.”<sup>98</sup> Moreover, courts have interpreted the

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<sup>89</sup> 21 U.S.C. § 353a(a) (exempting certain compounding activities from the reach of the FDCA sections 501(a)(2)(B) (adulteration), 502(f)(1) (misbranding), 505 (new drugs)); *but see Medical Ctr. Pharm.*, 536 F.3d at 405 (noting that because Congress started from a default premise that the FDCA’s “adulteration, misbranding, and new drug provisions apply to –and thereby restrict – all drugs created by any means,” including compounding, that the FDCA must reach compounding). However, it can be argued that the understanding of a future Congress regarding previously enacted legislation will “rarely override a reasonable interpretation of a statute that can be gleaned from its language.” *See Consumer Prod. Safety Comm’n v. GTE Sylvania, Inc.*, 447 U.S. 102, 118 n.13 (1980).

<sup>90</sup> Brief of the Appellant United States, *United States v. Franck’s Lab, Inc.*, 11-15350-BB (11<sup>th</sup> Cir 2012). at pg. 26.

<sup>91</sup> Food and Drug Administration, “Is It Really FDA Approved?,” press release, February 20, 2009, <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM143301.pdf>.

<sup>92</sup> Brief of the Appellant United States, *United States v. Franck’s Lab, Inc.*, 11-15350-BB (11<sup>th</sup> Cir 2012). at pg. 26; *see also Professionals & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593-594 (5<sup>th</sup> Cir. 1995).

<sup>93</sup> *Medical Ctr. Pharm.*, 536 F.3d at 399.

<sup>94</sup> *Id.*

<sup>95</sup> *See W. States Med. Ctr.*, 535 U.S. at 369 (“[R]equiring such testing would force pharmacists to stop providing compounded drugs.”)

<sup>96</sup> *See generally Franck’s Lab*, 816 F. Supp. 2d at 1235-1239 (discussing the cases that have examined the scope of the FDA’s authority with respect to compounding).

<sup>97</sup> *Id.*; *see also Med. Ctr. Pharm.*, 536 F.3d at 399 (“Construing the FDCA to give the FDA authority over compounding would thus not necessarily ‘lead to a result so bizarre that Congress could not have intended it.’”)(internal citations omitted); *In re Wedgewood Vill. Pharmacy*, 270 F. Supp 2d 525, 549 (D.N.J. 2003) (“Congress intended that the FDCA, both in its original form and as amended, allow the FDA broad enforcement powers to fulfill its mandate that it protect the public from unsafe medication.”)

<sup>98</sup> *Franck’s Lab*, 816 F. Supp. 2d at 1246.



FDA's 2002 CPG as a reasonable means by which the FDA can gauge whether an entity is engaged in manufacturing.<sup>99</sup>

However, a question remains as to whether a so-called “maximalist” interpretation of the FDA’s authority exists, such that any “traditional compounding” is “*per se* unlawful under the FDCA.”<sup>100</sup> In favor of the maximalist interpretation of the FDA’s authority over compounding is the plain language of the FDCA.<sup>101</sup> Specifically, the FDCA’s “new drug” provisions broadly state that no person can “introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed” pursuant to the statute with the FDA has occurred with respect to the drug.<sup>102</sup> Moreover, section 501 of the FDCA broadly deems a drug to be “adulterated” if it “is a drug and the” way it was manufactured, processed, packaged, or held does not conform with good manufacturing practices that ensure its quality and purity.<sup>103</sup> The FDCA’s misbranding provisions are equally broad, in that the statute deems a drug to be “misbranded” if its labeling does not bear “adequate directions for use.”<sup>104</sup> In none of the three aforementioned provisions does the FDCA’s plain language exempt traditional compounding activity from the act’s reach. As one court has noted, “[c]ompounded drugs are, after all, drugs,”<sup>105</sup> and therefore, the plain language of the statute would seem to indicate that compounding activities are within the purview of the FDA’s authority under the act.<sup>106</sup> Moreover, the maximalist interpretation is supported by the argument that because exemptions exist under the FDCA’s provisions for other types of drugs, such as “investigational drugs,”<sup>107</sup> one can presume from Congress’s refusal to create a general exemption for traditional compounding an implicit extension of federal authority over all forms of compounding.<sup>108</sup>

On the other hand, given the “ubiquity of pharmacy compounding at the time Congress passed the FDCA,” it can be argued that it would be absurd for Congress to have taken the “unprecedented” action to implicitly regulate compounded drugs through the 1938 act.<sup>109</sup> This argument is buttressed by Supreme Court case law on statutory interpretation that generally holds that it should not be assumed that Congress “alter[s] the fundamental details of a regulatory scheme in

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<sup>99</sup> See *Wedgewood Vill. Pharm.*, 421 F.3d at 272 (“We agree that the factors set forth in the CPG are reasonable and that they reflect the FDA’s ‘careful consideration ... over a long period of time.’”) (internal citations omitted).

<sup>100</sup> See *Franck’s Lab*, 816 F. Supp. 2d at 1239.

<sup>101</sup> The plain language of a statute is the starting point for statutory interpretation, and if a statute’s terms are “plain,” the Supreme Court has noted that a court should look no further and enforce the law “according to its terms.” See *Hartford Underwriters Ins. Co. v. Union Planters Bank, N.A.*, 530 U.S. 1, 6 (2000).

<sup>102</sup> 21 U.S.C. § 355(a).

<sup>103</sup> 21 U.S.C. § 351(a)(1)(B).

<sup>104</sup> 21 U.S.C. § 352(f)(1).

<sup>105</sup> *Medical Ctr. Pharm.*, 536 F.3d at 395.

<sup>106</sup> *Id.*; see also *United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176 (7<sup>th</sup> Cir. 1988) (holding, with respect to the misbranding provisions of the FDCA, “Congress gave the FDA comprehensive powers to license the manufacture of drugs and limit their sales,” leaving it to the discretion of the FDA to regulate bulk compounding); *United States v. Algon Chemical, Inc.*, 879 F.2d 1154, 1163 (3d Cir. 1989) (concluding that Congress did not intend that bulk drug compounding “be excluded from the Act’s labeling requirements”).

<sup>107</sup> 21 U.S.C. § 360b(j).

<sup>108</sup> *Medical Ctr. Pharm.*, 536 F.3d at 395; but see *Franck’s Lab*, 816 F. Supp. 2d at 1244 (“However, if we were to presume a delegation of power from the absence of an express withholding of such power, agencies would enjoy virtually limitless hegemony”) (internal citations and quotations omitted).

<sup>109</sup> *Id.* at 398 (summarizing the pharmacists’ position); see also *Franck’s Lab*, 816 F. Supp. 2d at 1243-44.

vague terms or ancillary provisions.”<sup>110</sup> Moreover, the legislative history of the FDCA appears to support the view that manufacturers were the intended target of the regulatory scheme imposed by the 1938 act.<sup>111</sup> For example, the then-President of the American Pharmaceutical Association testified before a Senate subcommittee in 1938 in support of the legislation that while the “regulations governing ... the practice of pharmacy are very strict ... the privileges of unlicensed persons operating outside of pharmacies are so extensive that the public enjoys little protection,”<sup>112</sup> evincing that Congress’s central concern with the FDCA was manufacturing, not traditional pharmacy compounding. Legislative history can guide a court in assessing the correct interpretation of the scope of the FDA’s authority under the act.<sup>113</sup>

The current limits of federal authority to regulate traditional drug compounding have been discussed by very few courts, and each court that has approached the issue did so from a unique factual setting that colored the eventual outcome of the case.<sup>114</sup> As a consequence, the precise limit to federal authority with respect to drug compounding remains uncertain, although Congress could arguably expand the scope of the FDCA to reach traditional compounding.<sup>115</sup> As a matter of policy, the FDA has generally declined to test the current limits of its authority to regulate compounding,<sup>116</sup> preferring to defer to state governments with respect to the regulation of “traditional compounding.”<sup>117</sup> As a result, absent further congressional action, the limits of the FDA’s authority to regulate all forms of compounding will likely continue to be unresolved.<sup>118</sup> With respect to enforcement efforts clearly within the FDA’s broad discretion, such as combating compounding that is akin to large-scale manufacturing, courts will likely provide considerable deference to the FDA.<sup>119</sup>

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<sup>110</sup> See *Whitman v. American Trucking Assoc.*, 531 U.S. 457, 458 (2001) (“[Congress] does not, one might say, hide elephants in mouseholes”); see also *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (“[W]e are confident that Congress could not have intended to delegate a decision of such economic and political significance to an agency in so cryptic a fashion.”)

<sup>111</sup> *Franck’s Lab*, 816 F. Supp. 2d at 1245-46.

<sup>112</sup> Food, Drugs and Comsetis: Hearings Before a Subcomm. of the Comm. on Commerce, 74 Cong. 100, 102 (1935) (statement of Robert P. Fischelis, president American Pharmaceutical Ass’n).

<sup>113</sup> See generally *Crandon v. United States*, 494 U.S. 152, 160 (1990).

<sup>114</sup> See generally *Franck’s Lab*, 816 F. Supp. 2d at 1235-1239 (discussing the cases that have examined the scope of the FDA’s authority with respect to compounding).

<sup>115</sup> See *Gonzales v. Raich*, 545 U.S. 1, 22 (2005) (holding that the authority under the Commerce Clause extends such that Congress can regulate activities when, taken in the aggregate, substantially affect interstate commerce).

<sup>116</sup> But see *Franck’s Lab*, 816 F. Supp. 2d at 1214 (“[T]he FDA has taken the bright-line position that any compounding of animal medications from bulk substances violates ... the FDCA ...”)

<sup>117</sup> See CPG § 460.200 (May 29, 2002); see also CPG § 608.400 (July 14, 2003).

<sup>118</sup> This lack of resolution could be a considerable burden on traditional compounders, whose conduct could be in violation of federal law. As one court noted, “it remains no small burden for compounding pharmacists ... to ‘live in sin,’ [as] their livelihood [has] no greater assurance than the FDA’s good graces.” See *Medical Ctr. Pharm.*, 536 F.3d at 399-400.

<sup>119</sup> See, e.g., *Wedgewood Vill. Pharm.*, 421 F.3d at 272-73.



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