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Stella Haeyoung Kim

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THE DRUG QUALITY AND THE SECURITY ACT OF 2013: COMPOUNDING CONSISTENTLY*

STELLA HAEYOUNG KIM**

I. INTRODUCTION

Starting in the summer of 2012, contaminated steroid injections compounded by the New England Compounding Center (“NECC”) were causing fungal meningitis.¹ By 2013, more than 800 people across twenty-three states were affected, resulting in sixty-four deaths.² Reminiscent of past public health crises of sulfanilamide and thalidomide,³ the NECC meningitis outbreak immediately demanded legislative action. A bill for reform was swiftly passed and on

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* The Journal of Health Care Law and Policy originally received this piece for publication in late 2015. At that time, publication delays prevented the timely release of this Comment. Both the Author and the Journal of Health Care Law and Policy recognize that since the original submission, FDA has released several guidance documents pertaining to compounding and has been exercising greater regulatory actions to address some of the concerns originally raised in this comment. Furthermore, individual states may have updated their laws and regulations to parallel the DQSA.

** Pharm.D., J.D., University of Maryland, 2016. This Note would not have been possible without the expertise, insight, and support of many wonderful people. I would like to first and foremost thank Dr. Frank Palumbo for lending me your expertise in compounding. More importantly, you always challenged me and had faith in me; I would not have made it through all five years without your guidance. Thank you to Professor Virginia Rowthorn, for you have been the best cheerleader throughout my law school career; thank you for your constant support. Thank you to Dr. Dan Le for your encouragement and words of wisdom. Thank you to Michael Vinluan for your steadfast friendship and mentorship. Thank you to Kelvin Lucas for lending me your skills at the last minute. Thank you to Mr. J. Kennelly for always being my first pair of eyes. Special thanks to the Journal of Health Care Law and Policy, especially Kelsey Harrer, Reena Palanivel, and Hassan Sheikh. Thank you to my family—Mom, Dad, Sung, Charly, Christy, and my three beautiful nieces Layla, Olivia, and Melia—for your patience and confidence in my endeavors. And last but not least, I dedicate this Note wholeheartedly to James and our Happiness.

1. STAFF OF H. COMM. ON ENERGY & COMMERCE, 113TH CONG., FDA’S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED OPPORTUNITIES? 1 (Comm. Print 2013) [hereinafter HOUSE STAFF REPORT]. Fungal meningitis is a life-threatening rare infection of the membrane that surrounds the brain and spinal cord. The more common etiologies of meningitis are bacterial and viral. Regardless, any type of meningitis is life-threatening and can be fatal if not treated immediately. *Meningitis*, CDC (Mar. 4, 2016), <http://www.cdc.gov/meningitis/index.html>.

2. Kurt Eichenwald, *Killer Pharmacy: Inside a Medical Mass Murder Case*, NEWSWEEK (Apr. 16, 2015), <http://www.newsweek.com/2015/04/24/inside-one-most-murderous-corporate-crimes-us-history-322665.html>; see also HOUSE STAFF REPORT, *supra* note 1.

3. See *infra* Part II.A.

November 27, 2013, President Barack Obama signed the Drug Quality and Security Act (“DQSA”), giving the United States Food and Drug Administration (“FDA”) direct authority over large-scale compounding.⁴ Overall, the DQSA is a direct response to the NECC crisis and its main purpose is to prevent another national compounded drug calamity from ever happening again.

To evaluate whether the DQSA will prevent history from repeating itself, this note is divided into four parts following this Introduction. Part II discusses significant historical events that incentivized changes in drug regulation and collectively provided an impetus for the DQSA. Part III delves into the current regulatory landscape of large-scale sterile compounding by examining FDA guidance documents on the standard that should be used for sterile compounding and how this compares to what the standard was before the DQSA. Part IV explores selected issues and implications that need further evaluation and clarification by FDA in order for the DQSA to successfully become what it was intended for and more—the safe production and distribution of customized medicine that has the potential to treat unique conditions and alleviate drug shortages. Lastly, Part V briefly summarizes the past, present, and hopeful future of drug compounding where it will be regulated routinely to produce consistently sterile compounded drugs for safe patient use.

II. REGULATORY JURISDICTION

Before the DQSA, the regulatory jurisdiction regarding drug compounding was inconsistent due to amendments, regulations, and conflicting case rulings. Furthermore, the landscape of health care was changing. Compounds—once a mainstay of healthcare—became second-tier for an extended period of time until they resurfaced as efficient alternatives to unavailable yet necessary treatments customized for patients with special needs. Policies had to adapt, but these were inefficient and ineffective because every change only caused unnecessary conflict and greater confusion. This section discusses the regulatory landscape pre-DQSA and post-DQSA to explain how the regulatory landscape changed since 1938 until the passage of the DQSA, which made the landscape more uniform and clearer than before.

A. Pre-DQSA: No One Had Explicitly Clear Regulatory Authority over Compounding

Before the DQSA, the regulation of compounding progressively became complicated as compounded drugs became a prominently different category of drugs than commercially manufactured drugs.⁵ Traditionally, drugs were com-

4. H.R. 3204, 113th Cong. (2013) (enacted).

5. See *infra* notes 29–30 and accompanying text.

pounds concocted by pharmacists by combining and mixing different drug ingredients or altering a drug for a specific patient or indication.⁶ Drug regulation was minimal and FDA did not exist until 1930.⁷

Significant federal regulation of drugs began in 1938 when Congress passed the Food, Drug, and Cosmetic Act (“FDCA”), delegating authority to FDA to oversee the safety of food, drugs, and cosmetics.⁸ This act was passed in response to the 1937 sulfanilamide disaster during which more than one hundred people died.⁹ S.E. Massengill, a drug manufacturer, seized a commercial opportunity to make and ship out a total of 633 shipments of sulfanilamide in a new, liquid form.¹⁰ Regrettably, the company failed to test the product for safety—it turned out that the solvent used, diethylene glycol, was a poisonous chemical.¹¹ Thus, the FDCA was quickly passed to ensure that “the distribution of highly potent drugs . . . be controlled by an adequate Federal Food and Drug law.”¹² After 1938, manufacturers had to get pre-market approval from FDA, which meant that drugs now had to be safe *prior* to marketing.¹³ The FDCA of 1938, however,

6. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-13-702, DRUG COMPOUNDING: CLEAR AUTHORITY AND MORE RELIABLE DATA NEEDED TO STRENGTHEN FDA OVERSIGHT 1 (2013) [hereinafter GAO COMPOUNDING REPORT] (“Drug compounding is the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a drug tailored to the medical needs of an individual patient.”). There are many other definitions of “compounding” by different organizations that vary in how inclusive or specific it wants to be. For example, the International Academy of Compounding Pharmacists defines “compounding” as the preparation of a customized medication that is not commercially available. *Compounding FAQs*, IACP, <http://www.iacprx.org/?page=2> (last visited Jan. 6, 2016). The emphasis is on being unattainable as a manufactured drug. GAO’s definition emphasizes the aspect of being a “tailored” medication. DQSA defines compounding to “include[] the combining, admixing, mixing, diluting, pooling, reconstituting, or other altering of a drug or bulk drug substance to create a drug.” 21 U.S.C. § 353b(d)(1) (2013). DQSA lists the different acts of compounding “to create a drug.” The emphasis is on creating a drug; therefore, it needs to be regulated by FDA.

7. The Pure Food and Drugs Act of 1906 was “vague and less than what . . . supporters of federal food and drug regulation had hoped for,” but it did establish the first federal food and drug regulation that was originally headed by the Bureau of Chemistry. It was not until 1927 when the Bureau of Chemistry was divided into two departments, one of which was titled the Food, Drug, and Insecticide Administration (“FDIA”). In 1930, FDIA shortened to FDA. Andrea T. Borchers et al. *The History and Contemporary Challenges of the US Food and Drug Administration*, 29 CLINICAL THERAPEUTICS 1, 4, 6 (2007).

8. ANDREW NOLAN, CONG. RESEARCH SERV., R43038, FEDERAL AUTHORITY TO REGULATE THE COMPOUNDING OF HUMAN DRUGS 2 (2013); *see also* Pub. L. No. 75-717, 52 Stat. 1040 (1938) (current version at 21 U.S.C. § 355(a) (2006)) (giving FDA authority over the approval of “new drug” products into interstate commerce).

9. Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG. (Jun. 1981), <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>.

10. At the time, sulfanilamide was only available as tablet or powder form and when the liquid form was tested, it was only tested for flavor, appearance, and fragrance. *Id.*

11. Diethylene glycol is normally used as antifreeze. *Id.*

12. *Id.* (quoting FDA Commissioner Walter Campbell).

13. 21 U.S.C. §§ 331(d), 355(a) (2006).

did not specifically address the act of drug compounding by pharmacists in pharmacies separate from manufacturing drugs.¹⁴

Compounding was first mentioned in the Kefauver-Harris Drug Amendments of 1962 (“Kefauver-Harris Amendments”)¹⁵ that were enacted in response to yet another drug catastrophe: the thalidomide crisis.¹⁶ Thalidomide was used as an anti-emetic for pregnant women suffering from morning sickness.¹⁷ The drug caused major birth defects in the children of women who took thalidomide during their first trimesters of their pregnancies.¹⁸ In the 1950s, it was believed that mother and fetus were two individual entities, completely separated by an impermeable placenta.¹⁹ Relying on this erroneous belief, drug manufacturers did not study the teratogenicity of their drugs.²⁰ Moreover, under the FDCA of 1938, showing that a drug was safe for use was almost unnecessary because if FDA did not decide on an application of a new drug in the allotted time, the drug automatically got approved.²¹ The detrimental effects of thalidomide proved that the FDCA of 1938 needed an update.

14. *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing Before the S. Comm. on Health, Educ., Labor, & Pensions*, 108th Cong., 41 (2003) [hereinafter *2003 Congressional Hearing*] (statement of Steven K. Galson, Deputy Director, Center for Drug Evaluation & Research, U.S. Food & Drug Admin.) (recognizing that the FDCA of 1938 had “no provisions specifically dedicated to compounding, as distinguished from manufacturing of drugs”); see also NOLAN, *supra* note 8, at 2.

15. Pub. L. No. 87-781, 76 Stat. 780, 792–93 (1962) (current version at 21 U.S.C. § 374(a)(2) (2006)) (using “compound” within a group of words to describe drug preparation: “manufacture, prepare, propagate, compound, or process drugs.”).

16. Jerry Avorn, *Learning About the Safety of Drugs—A Half-Century of Evolution*, NEW ENG. J. MED. 2151, 2153 (2011) (recognizing that the devastating effects of thalidomide seen around the world accelerated the Kefauver-Harris Amendments, “setting the stage for new authority for the FDA for decades to come”).

17. *Id.* at 2152. In the United States, FDA never approved thalidomide, but women were able to obtain the popular drug while traveling abroad to Europe, Australia, and Canada or from their doctors who received samples for company-sponsored studies in pursuit of FDA approval. *Id.* at 2153. The American drug company that was manufacturing thalidomide at the time distributed more than 2.5 million thalidomide tablets to 1267 doctors who then distributed the drug to about 20,000 pregnant patients leading to seventeen affected infants in the United States. George J. Annas & Sherman Elias, *Thalidomide and the Titanic: Reconstructing the Technology Tragedies of the Twentieth Century*, 89 AM. J. PUB. HEALTH, 98, 99 (1999).

18. Avorn, *supra* note 16, at 2152 (describing infants being born with severe limb deformities where hands or feet were directly emerging from their torsos).

19. Deborah A. Goldman, *Thalidomide Use: Past History and Current Implications for Practice*, 28 ONCOL. NURS. FORUM, 471, 472 (2001) (discussing how pregnant women in the 1950s were not warned against the effects of drugs or alcohol because it was believed that nothing crossed the placenta to harm the fetus).

20. *Id.*

21. Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAG., CENTENNIAL ED. (2006), <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm>.

After the Kefauver-Harris Amendments, drugs had to be safe *and* effective.²² Effectiveness is how well a drug works for its intended use, proven by extensive research and clinical trials that test the drug in different subgroups of the population.²³ Under this definition, thalidomide as an anti-emetic for pregnant women is an ineffective and unsafe drug because thalidomide crosses the placenta, causing irreversible harm to the developing fetus.²⁴ Safety and effectiveness has to be demonstrated together for FDA to evaluate the risks and benefits of approving a new drug for its intended use.²⁵

However, pharmacies that compounded were exempt from the requirements of proving safety and effectiveness of a product before it went to market as long as the compound was made in response to a physician's prescription and within "the regular course of [the pharmacy's] business of dispensing or selling drugs . . . at retail."²⁶ Moreover, FDA delegated the regulation of compounding to the states: "The provisions . . . shall not apply to pharmacies which maintain establishments in conformance with any applicable *local* laws regulating the practice of pharmacy"²⁷ This set up a dichotomy of regulating drug distributors in the United States. FDA regulated the manufacturing of drugs and states regulated the compounding of drugs until the passage of the DQSA in 2013.²⁸

1. Return of Pharmacy Compounding Instigated FDA's Attempt to Reclaim Its Regulatory Authority

Once the main method of creating a drug, compounding took a backseat when commercial manufacturing of drugs became more efficient and popular in

22. Pub. L. No. 87-781, 76 Stat. 780 (1962) (current version at 21 U.S.C. § 321(p) (2006)) (inserting the words, "safety" and "effectiveness" into the definition of a "new drug"); *see generally* 21 U.S.C. § 351(a) (2006) (detailing what an adulterated drug is and stating that such a drug would be considered unsafe for consumer use).

23. 21 U.S.C. § 355(d) (2006) (defining effectiveness of a drug as the evaluation of "substantial evidence" that "consist[s] of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience" who can "fairly and responsibly" conclude that "the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof").

24. Goldman, *supra* note 19, at 472. Thalidomide is still on the market today, but to treat leprosy and certain types of cancer. For cancer patients, the risks outweigh the benefits of using thalidomide. *Id.* at 471.

25. In order for a new drug to be marketed in the U.S., it must be approved by FDA through a New Drug Application ("NDA"). In a NDA, the manufacturer must provide details of the drug's safety and effectiveness for its proposed indication(s) through extensive clinical trials; whether the benefits outweigh the risks; and methods use to demonstrate the preservation of the drug's identity, strength, quality, and purity. 21 C.F.R. § 314.50 (2015); *see also* *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm> (last updated Feb. 3, 2015).

26. 21 U.S.C. § 374(a)(2)(A) (2006). *But see infra* Part II.A.2.

27. 21 U.S.C. § 374(a)(2)(A) (2006) (emphasis added).

28. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362 (2002) ("For approximately the first 50 years after FDCA, FDA generally left regulation of compounding to the States.").

the 1960s.²⁹ However, the demand for compounds began to re-emerge in the 1980s and 1990s, as drugs were becoming short in supply and complicated disease states called for customized medications.³⁰ The number of large-scale compounding pharmacies increased to cater to these demands.³¹ These pharmacies began to blur the line between compounding and conventional manufacturing by either reproducing exact copies of commercially available products, using unapproved or withdrawn³² active ingredients, and/or producing large quantities that often involved interstate commerce.³³ Although FDA delegated authority over compounding to the states due to the assumption that compounds were done in small quantities within individual state borders,³⁴ the expansion of pharmacy compounding prompted FDA to exercise its authority through various lawmaking actions.

First, in response to the increase of borderline manufacturing practices by compounders, FDA issued the Compliance Policy Guide in 1992 (“1992 CPG”), which listed nine factors FDA would consider when assessing whether a compounder was acting like a manufacturer.³⁵ If a compounder was determined to be

29. Roy Guharoy, et al. *Compounding Pharmacy Conundrum: “We Cannot Live Without Them but We Cannot Live With Them,”* 143 CHEST 896, 896 (2013) (noting that approximately 80% of prescriptions were compounded in the 1950s, then “the paradigm changed in the 1960s with the commercial availability of many products, and pharmacy practice gradually transitioned to dispensing of FDA-approved commercial products”).

30. *Id.*; see also Patrick J. Coyne et al., *Compounded Drugs: Are Customized Prescription Drugs a Salvation, Snake Oil, or Both?*, 8 J. HOSPICE & PALLIATIVE NURSING 222, 222 (2006) (noting that compounding has been increasing in the past 20 years due to increase in demand for home health care, total parenteral nutrition, and pain management in hospice care); see also David Brown, *Compounding Pharmacies Rise in Popularity but Bring Questions About Safety*, WASH. POST (Oct. 13, 2012), https://www.washingtonpost.com/national/health-science/compounding-pharmacies-rise-in-popularity-but-bring-questions-about-safety/2012/10/13/e87f8cc2-14a0-11e2-ba83a7a396e6b2a7_story.html (noting the continued popularity in compounding into the 21st century, “driven by the rise of out-of-hospital surgical care, the high prices and shortages of drugs, and the real or imagined benefit of ‘personalized medicine’”).

31. GAO COMPOUNDING REPORT, *supra* note 6, at 5–6 (reporting that although the exact number of compounding is unknown, IACP estimated that in 2013, compounding made up about one to three percent of the U.S. prescription drug market and there has been an increase in hospitals outsourcing for drug compounding in the last decade, estimating that nearly all hospitals outsource for sterile compounded products).

32. Withdrawn active ingredient drugs are those that are taken off the market by FDA due to safety or effectiveness reasons. 21 U.S.C. §§ 353a(b)(1)(C), 353b(a)(4) (2006).

33. *2003 Congressional Hearing, supra* note 14, at 6, 38, 39 (2003) (statement of Steven K., Acting Director, Center for Drug Evaluation & Research, U.S. Food & Drug Admin.) (recognizing that with the growth of compounding included true medical needs for compounding, but also purely economic reasons where pharmacies were compounding drugs that were removed from the market or exact copies of commercially available drugs, selling them at low costs in large amounts and making hefty profits).

34. Kevin Outterson, *Regulating Compounding Pharmacies after NECC*, 367 NEW ENG. J. MED. 1969, 1971 (2012) (stating that Congress recognized states as capable of effectively regulating traditional compounding pharmacies because of the smaller volume and lack of interstate commerce).

35. *Thompson v. W. States Med. Ctr.*, 535 U.S. at 363 (citing U.S. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDE 7132.16, MANUFACTURE, DISTRIBUTION AND PROMOTION OF

manufacturing instead of compounding, FDA could choose from a range of enforcement actions that included issuing warning letters, injunctions, and even criminal charges.³⁶ The 1992 CPG was an enforcement tool for FDA.

Many pharmacies and pharmacy organizations were upset with the more extensive federal oversight outlined in the 1992 CPG.³⁷ In *Professionals & Patients for Customized Care v. Shalala*, the plaintiff argued that the 1992 CPG was invalid because it did not go through the proper administrative procedure to become an enforceable rule.³⁸ The Fifth Circuit held otherwise, stating that the 1992 CPG was a valid statement of policy or an interpretive rule, which did not need to be processed through administrative procedures.³⁹

To inarguably solidify FDA's role of regulating compounding, Congress passed the Food and Drug Administration Modernization Act ("FDAMA") of 1997 with the 1992 CPG incorporated into it.⁴⁰ The FDAMA amended the FDCA by creating Section 503A, titled "Pharmacy Compounding."⁴¹ This provision states that a compound is technically a new drug, but it will be exempt from FDA regulation as long as the outlined conditions are followed.⁴² Under the FDAMA, compounding is valid as long as a licensed pharmacist or doctor compounds the drug using approved ingredients for an identifiable patient with a receipt of a

ADULTERATED, MISBRANDED, OR UNAPPROVED NEW DRUGS FOR HUMAN USE BY STATE-LICENSED PHARMACIES (Mar. 16, 1992) [hereinafter 1992 CPG]; see also *infra* note 56 and accompanying text.

36. *Thompson v. W. States Med. Ctr.*, 535 U.S. at 363; see also U.S. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDE 460.200, PHARMACY COMPOUNDING 4 (May 29, 2002) [hereinafter 2002 CPG].

37. *Outterson*, *supra* note 34, at 1969 (noting that the 1992 CPG "attracted enough criticism that Congress created a safe-harbor compounding statute in 1997, amending the FDCA with a new section, 503A").

38. 56 F.3d 592, 595 (5th Cir. 1995) (alleging that the 1992 CPG was invalid because it did not satisfy the notice-and comment requirements of the Administration Procedure Act).

39. *Id.* at 602.

40. GAO COMPOUNDING REPORT, *supra* note 6, at 7.

41. Pub. L. No. 105-115, 111 Stat. 2296, 2328 (1997) (codified at 21 U.S.C. § 353a (2006)) (amending Chapter V of Title 21 and adding a section specifically for pharmacy compounding).

42. A compounded drug will be exempt from manufacturing requirements of §§ 351(a)(2)(B), 352(f)(1), and 355 as long as the drug is compounded for "an identified individual patient based on the unsolicited 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" and the compound is prepared by a licensed pharmacist or physician. 21 U.S.C. § 353a(a). Furthermore, a compound may be prepared in advance of a valid prescription as long as it is prepared by a licensed pharmacist or physician in limited quantities and based on a history of receiving such valid prescription orders as well as on an established relationship between the licensed compounder and the individual patient or the practitioner writing the prescription. *Id.*

valid prescription.⁴³ Moreover, the compound could not be advertised or promoted⁴⁴ or be a copy of a commercially available product, listed in the Federal Register of withdrawn unsafe drugs, or compounded in excessive amounts.⁴⁵

Under the new law, the main difference between compounding and manufacturing was that there needed to be a pre-existing valid prescription for a compound to be made; a compound could not be made before the receipt of an order whereas manufacturing could be done in large quantities without prescriptions.⁴⁶ As long as compounders followed this general rule, they were regulated by the state.⁴⁷ Once they showed signs of “manufacturing,” FDA would step in and take over authority in a similar fashion outlined by the 1992 CPG.⁴⁸

However, the validity of Section 503A was brought to issue for the next few years. In 2001, a group of pharmacies in *Western States Medical Center v. Shalala* challenged Section 503A, arguing that the prohibition against advertising their products was a violation of their First Amendment free speech rights.⁴⁹ The Ninth Circuit ruled in their favor and held that this specific subsection of Section 503A was invalid.⁵⁰ However, the Ninth Circuit decided that the rest of the section was not severable; thus, all of Section 503A had to be made invalid.⁵¹ The Court reasoned, “[a] statute’s constitutional provisions are not severable if the entire statute is designed to strike a balance between competing interests”—meaning manufacturers and compounders.⁵²

43. *Id.*

44. Although pharmacies could not advertise compounded products, letting the public know of their services was not prohibited. Pub. L. No. 105-115, 111 Stat. 2296, 2330 (1997), *repealed by* Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587, 598 (2013) (striking subsection on advertising of compounded drug products).

45. Pub. L. No. 105-115, 111 Stat. 2296, 2329 (1997) (current version at 21 U.S.C. §§ 353a (2013)).

46. *See supra* note 25 and accompanying text.

47. *See supra* note 26 and accompanying text.

48. GAO COMPOUNDING REPORT, *supra* note 6, at 7.

49. 238 F.3d 1090, 1092 (9th Cir. 2001) (contending that the government cannot regulate commercial speech therefore making the FDAMA unconstitutional).

50. *Id.* at 1096 (holding that the free speech restrictions of the FDAMA are “more extensive than necessary” and “[t]he First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good”) (quoting 44 Liquormart v. R.I., 517 U.S. 484, 503 (1996)).

51. *W. States Med. Ctr. v. Shalala*, 238 F.3d at 1096 (opining that “Sections 353a(a) and (c) cannot be severed from the rest of the FDAMA unless Congress would have enacted the constitutional provisions of the FDAMA absent the unconstitutional provisions”).

52. *See id.* (looking to the FDAMA’s legislative history to show that Congress had good intentions to make compounded drugs accessible to the public while “preventing pharmacies from making an end run around the FDA’s drug manufacturing requirements”).

A year later, the Supreme Court in *Thompson v. Western States Medical Center* affirmed the Ninth Circuit's holding that advertising restrictions were unconstitutional.⁵³ However, the Supreme Court remained silent as to the severability issue that the Ninth Circuit ruled on in *Western States Medical Center v. Shalala*.⁵⁴ As a result, the Ninth Circuit continued to uphold that all of Section 503A was invalid, thereby rendering FDA's regulatory authority in the Ninth Circuit nearly extinct.

To regain its authority over compounding, FDA updated the CPG in 2002 ("2002 CPG").⁵⁵ Like its predecessor, the 2002 CPG listed nine factors that would demonstrate when a pharmacy was engaged in manufacturing and not compounding.⁵⁶ The 2002 CPG, similar to Section 503A, emphasized that FDA would only take action against pharmacies that were suspected of manufacturing instead of compounding and deferred the rest of compounding matters to the States.⁵⁷ As a result, the Ninth Circuit could no longer rely on Section 503A as a legally binding authority; instead, it only had the non-legally binding FDA guidance of the 2002 CPG to assist FDA's authority to identify and reprimand manufacturing compounders.

The situation became more complicated after the Fifth Circuit rejected the Ninth Circuit's holding of non-severability in *Medical Center Pharmacy v. Mukasey*.⁵⁸ The Fifth Circuit held that the provision banning advertising was invalid and indeed severable from the rest of Section 503A, making the rest of the provisions valid.⁵⁹ The Court reasoned that "[u]nless it is evident that the Legis-

53. *Thompson v. W. States Med. Ctr.*, 535 U.S. at 377 (holding that forbidding advertising would affect not just large-scale compounders, but everyday pharmacists with good intentions of trying to provide exceptional health care, such as when a pharmacist wants to inform a parent of the different flavorings that can be added to a child's medicine to make it more tasty or informing doctors about different ways a drug can be compounded so a patient who is unable to swallow a tablet can take the medicine more easily).

54. *See id.* at 360 (noting that because petitioners challenged only the constitutional holding of the Court of Appeals' decision and the respondents did not cross-petition, the Court only addressed the First Amendment issue and not the severability issue).

55. GAO COMPOUNDING REPORT, *supra* note 6, at 8.

56. The nine non-exhaustive factors assesses whether the compound: (1) was done in anticipation of a prescription order; (2) is a copy of a drug that has been withdrawn or removed from the market; (3) is prepared from bulk ingredients; (4) was prepared without a written assurance from the supplier that each drug substance was made in FDA-registered facility; (5) used drug components not in compliance with official compendia requirements; (6) used commercial scale manufacturing or testing equipment; (7) was prepared for third parties who resell the drugs; (8) is just a copy of a commercially available drug; and (9) was prepared by complying with applicable state law. 2002 CPG, *supra* note 36, at 3–4.

57. *Id.* at 3.

58. 536 F.3d 383, 404 (5th Cir. 2008) (rejecting the Ninth Circuit's reliance on legislative history that Congress would not have enacted FDAMA without the advertising provisions because Congress made many other provisions to address FDA concerns of illegal large-scale compounding and restricting advertising was just one of those ways).

59. *Id.* at 405.

lature would not have enacted those provisions which are within its power, independently of that which is not, the invalid part may be dropped if what is left is fully operative as law.”⁶⁰

After the Fifth Circuit ruling in *Medical Center Pharmacy*, the country was divided as to the validity of Section 503A and the regulation of pharmacy compounding.⁶¹ States within the Ninth Circuit⁶² did not honor Section 503A and so followed the 2002 CPG.⁶³ States within the Fifth Circuit⁶⁴ only invalidated the ban on advertising of Section 503A and thus followed the rest of the provisions and the 2002 CPG.⁶⁵ The rest of the states had to reconcile the decisions of the Fifth and Ninth Circuits to determine FDA’s authority over pharmacy compounding.⁶⁶ This three-way split set up a confusing and perhaps arbitrary landscape for compounding regulation, perpetuating delay of enforcement action by FDA.⁶⁷ Despite forty years since the passage of the Kefauver-Harris Amendments, the regulation of pharmacy compounding was still in question. There lacked a uniform national law pertaining to compounding drugs, which set up a dangerous foundation for unregulated compounding.

2. FDA Had Authority Over Pharmacy Compounding Under FDCA, But Remained Cautious

Regardless of the conflicting regulatory landscape of state versus federal authority over compounding, FDA had authority over large-scale compounding because compounds are drugs and the FDCA generally gives FDA authority over all drugs.⁶⁸ Case law also supports FDA’s authority over large-scale compounding.⁶⁹ However, FDA remained cautious with NECC leading up to the 2012 events because of the conflicting regulatory landscape.⁷⁰

60. See *id.* at 401–02 (quoting *Alaska Airlines, Inc. v. Brock*, 480 U.S. 678, 684 (1987) (internal quotation omitted) (reasoning that the intent of Congress was made clear in FDCA § 391, which addresses severability: “any provision of this chapter . . . declared unconstitutional, or the applicability thereof to any person or circumstances is held invalid, the constitutionality of the remainder of the chapter and the applicability thereof to other persons and circumstances shall not be affected thereby”).

61. GAO COMPOUNDING REPORT, *supra* note 6, at 8, 36.

62. Alaska, Arizona, California, Hawaii, Idaho, Montana, Nevada, Oregon, and Washington.

63. GAO COMPOUNDING REPORT, *supra* note 6, at 36.

64. Louisiana, Mississippi, and Texas.

65. See *supra* text accompanying note 59.

66. GAO COMPOUNDING REPORT, *supra* note 6, at 36 (noting that in the majority of the country, FDA used criteria from both Section 503A and the 2002 CPG to assist in its determination of whether it would take enforcement action or not on compounding pharmacies).

67. See *infra* Part II.A.2.

68. 21 U.S.C. § 374(a)(1). See *infra* text accompanying note 81.

69. See *infra* text accompanying notes 85–87.

70. See *supra* Part II.A.1.

FDA was affected by the split landscape, being “too cautious because of fears of litigation that might actually further undermine [its] ability to apply authorities and take enforcement actions”⁷¹ FDA’s internal confusion and caution about its authority over compounding is best demonstrated by looking at the history between NECC and FDA that ultimately led to the agency’s inaction and NECC’s continued production of unsafe compounded drugs.

FDA knew about NECC’s illegitimate practices since 2002 through reported adverse events involving steroid injections that were causing meningitis-like symptoms.⁷² Subsequently, FDA inspected NECC three times by 2004.⁷³ However, it was not until December 2006 that FDA finally issued a warning letter mandating the owner of NECC, Barry Cadden, to “promptly correct these deviations” or face regulatory action, including seizure or injunction.⁷⁴ Before the warning letter was sent, FDA did not know whether inspecting NECC was appropriate, which further delayed FDA acting on the new complaints and reports of adverse events for different compounds made by NECC.⁷⁵ After receiving Mr. Cadden’s response to the warning letter one month later, FDA then questioned whether it was appropriate to inspect NECC before responding to Mr. Cadden.⁷⁶ Even after FDA finally replied to Mr. Cadden in November 2008, it continued to postpone inspections for unknown reasons.⁷⁷ However, an internal email reveals that FDA’s delay may have been due to the split regulatory landscape—Massachusetts was one of the states that had to reconcile the Fifth and Ninth Circuit decisions.⁷⁸ If FDA were to inspect NECC, it wanted to make sure NECC would satisfy the criteria for manufacturing outlined in the 2002 CPG and did not qualify for the exemptions of FDA oversight outlined in Section 503A so that NECC could not file a petition against FDA.⁷⁹ Consequently and unfortunately, no further inspections were made until the 2012 meningitis outbreak.⁸⁰

71. *A Continuing Investigation into the Fungal Meningitis Outbreak and Whether it Could Have Been Prevented: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 113th Cong., 59 (2013) [hereinafter *Meningitis Outbreak 2013 House Hearing*] (statement of Margaret A. Hamburg, Commissioner, U.S. Food & Drug Admin.).

72. HOUSE STAFF REPORT, *supra* note 1, at 7.

73. *Id.* at 7–8.

74. *Id.* at 10.

75. *Id.* at 11.

76. *Id.* at 13, 16.

77. *Id.* at 18.

78. *See id.* at 18–19 (recognizing that NECC could file a petition against FDA if FDA could not definitively demonstrate that NECC “fell outside the safe harbor provided to traditional compounding pharmacies under section 503A”).

79. *Id.*

80. *See id.* at 3 (noting that FDA failed to take any enforcement actions against NECC because it “has been grappling with its authority over compounding for decades” and it let that “uncertainty to essentially paralyze the agency’s oversight efforts from 2009 to 2012”).

Whether FDA had the authority to inspect a compounding pharmacy outside of the Fifth and Ninth Circuits pre-DQSA can be assessed by first looking at the FDCA. The FDCA generally gives FDA the authority to inspect any establishment where “food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held”⁸¹ However, pharmacy records are off-limits if the pharmacy is in compliance with local laws that regulate the practice of pharmacy.⁸² Under the plain reading of the FDCA, FDA has the authority to enter and inspect any compounding pharmacy upon reasonable and appropriate qualifications.⁸³ FDA used this authority to inspect a number of compounding pharmacies in the past,⁸⁴ as exemplified in a Third Circuit case from 2005.

In *Wedgewood Village Pharmacy, Inc. v. United States*, the Third Circuit held that the text of the FDCA clearly authorizes FDA to inspect compounding pharmacies.⁸⁵ The Court stated that although the 2002 CPG has no legal authority, “FDA need only show that the factors outlined in the CPG for determining compounding are a reasonable basis upon which to initiate an inspection under the FDCA.”⁸⁶ According to the Third Circuit, even though Section 503A was replaced by FDA-created guidelines of the 2002 CPG, FDA still had legitimate authority to inspect compounding pharmacies if it suspected the manufacturing of drugs.⁸⁷

Although *Wedgewood* was decided in 2005—three years before the Fifth Circuit split from the Ninth Circuit—*Wedgewood* reveals an important concept: the Third Circuit Court was willing to give great deference to FDA when the issue concerned drugs since the FDCA gives FDA oversight of all drugs.⁸⁸ If *Wedgewood* was decided post-Fifth and Ninth Circuit split, the decision most likely would not have changed due to the Court’s reliance on FDA’s expertise. It was inconsequential whether or not Section 503A was valid because the Court

81. 21 U.S.C. § 374(a)(1) (2006).

82. 21 U.S.C. § 374(a)(2)(A) (2006).

83. 21 U.S.C. § 374(a)(1) (2006) (stating that in order for an inspection officer to enter and inspect a facility, he/she shall present with proper credentials and a written notice for the owner of the facility).

84. GAO COMPOUNDING REPORT, *supra* note 6, at 8; *see also* HOUSE STAFF REPORT, *supra* note 1, at 6 (noting that “FDA has consistently asserted authority over compounding pharmacies engaged in activities more analogous to those of a drug manufacturer”).

85. *Wedgewood Vill. Pharm., Inc. v. United States*, 421 F.3d 263, 270 (3rd Cir. 2005).

86. *Id.* at 272–73.

87. *Id.* *Wedgewood Pharmacy* was suspected and found to be manufacturing instead of compounding because “Wedgewood’s operations exceeded those of a retail pharmacy.” *Id.* at 265–66. These activities included producing drug products in large amounts without patient-specific prescriptions, purchasing an encapsulation machine that is used for large-scale drug manufacturing, and purchasing bulk quantities of substances that exceeded the usual amount for a retail pharmacy. *Id.* at 265.

88. *See supra* text accompanying notes 81, 85.

held that the 2002 CPG was highly indicative of FDA's role in regulating pharmacies that were acting like manufacturers.⁸⁹ In the First Circuit, where NECC was located, FDA most likely had the authority to inspect NECC without much difficulty. However, FDA was conflicted, hesitant, and perhaps even apprehensive about the consequences of taking action in a split landscape between the Fifth and Ninth Circuits.⁹⁰

B. Post-DQSA: FDA Has Explicitly Clear Authority Over Large-Scale Compounding

The NECC incident underscored the need for clear authority and defined roles. Although FDA had the authority to inspect and enforce action on NECC, there remained enough doubt to deter the agency from taking decisive action.⁹¹ FDA needed and wanted explicit authority, such as requiring facilities like NECC to register with FDA to clearly place NECC under FDA oversight.⁹² In response to the NECC scandal, FDA Commissioner Margaret Hamburg adamantly declared, “[W]e must do everything we can to clarify and strengthen FDA’s authority in this area. We recommend that Congress recognize the appropriate state role in regulation of traditional compounding while authorizing clear and appropriate Federal standards and oversight needed for non-traditional compounders that produce riskier products.”⁹³ All the events leading up to 2012 impelled Congress to pass the DQSA, which unequivocally delegates oversight of large-scale compounding to FDA.⁹⁴

The DQSA generally amends the FDCA in two parts: Title I, the “Compounding Quality Act” (“CQA”) and Title II, the “Drug Supply Chain Act” (“DSCSA”).⁹⁵ This note analyzes only Title I of the DQSA. Title II addresses the need for electronically tracking drug products within the supply chain to ultimately deter and prevent “counterfeit, stolen, contaminated, or otherwise harmful” drug products being exposed to consumers,⁹⁶ and is beyond the scope of the topic for this note.

89. *Wedgewood*, 421 F.3d at 272–73.

90. *See supra* notes 71, 80.

91. *See supra* notes 75–80 and accompanying text.

92. *Meningitis Outbreak 2013 House Hearing* (statement of Margaret A. Hamburg, Commissioner, U.S. Food & Drug Admin.), *supra* note 71, at 30 (“[D]espite the ambiguities and the split court decision, compounding pharmacies are not required to register with [FDA], so we don’t know who they are and what they are making.”).

93. *Id.* at 24.

94. T.R. Goldman, *Health Policy Brief: Regulating Compounding Pharmacies*, HEALTH AFF., May 1, 2014, at 2, 3 (describing that the NECC crisis prompted “several rounds of both House and Senate committee hearings”).

95. Pub. L. No. 113-54, 127 Stat. 587 (2013) (codified in scattered sections of 21 U.S.C. 301 et seq.).

96. *Drug Supply Chain Security Act (DSCSA)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm> (last updated Feb. 29, 2016). *See generally* 21 U.S.C. § 360eee (2013).

Section 503A, which has minor changes from the DQSA,⁹⁷ addresses traditional pharmacy compounding, in which a drug product is compounded on an individual basis.⁹⁸ Traditional compounding occurs when a licensed pharmacist at a licensed pharmacy mixes drug ingredients upon receipt of a valid prescription for a specifically identified patient.⁹⁹ The DQSA changes the FDCA by adding Section 503B, creating a new category of an “outsourcing facility” focused on producing and distributing sterile compounds on a larger scale.¹⁰⁰ An outsourcing facility differs from a traditional 503A compounding pharmacy in that an outsourcing facility does not need to be a licensed pharmacy nor does it have to compound on an individual basis.¹⁰¹ The only vestige of traditional pharmacy that remains is the need for a licensed pharmacist to be present in the facility, supervising the on-site compounding.¹⁰² With the passage of the DQSA, this note turns to an examination of FDA guidance documents to determine whether the issues of jurisdiction and FDA authority have actually been resolved.

1. FDA Guidance Defines and Clarifies Its Direct Authority over Outsourcing Facilities

There are several guidance documents available manifesting FDA’s apparent authority over outsourcing facilities.¹⁰³ Of these, there are three separate guidelines just on the topic of registering as an outsourcing facility. One describes the process of registration,¹⁰⁴ another describes the fees associated with registration and inspection,¹⁰⁵ and the third outlines how an entity should decide whether to register as an outsourcing facility in the first place.¹⁰⁶ FDA makes very clear that once an entity registers as an outsourcing facility, FDA will have complete oversight.

97. See *supra* note 44.

98. 21 U.S.C. § 353a (2013).

99. 21 U.S.C. § 353a (2013); see also *supra* note 6 and accompanying text.

100. 21 U.S.C. § 353b(d)(4)(A) (2013).

101. 21 U.S.C. § 353b(d)(4)(A)(ii) (2013) (defining an “outsourcing facility” as a facility that “has elected to register as an outsourcing facility”) (emphasis added); 21 U.S.C. § 353b(d)(4)(C) (2013) (“An outsourcing facility may or may not obtain prescriptions for identified individual patients.”).

102. 21 U.S.C. § 353b(a) (2013).

103. *Regulatory Policy Information*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucml66743.htm> (last visited April 24, 2016).

104. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: REGISTRATION OF HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT (Nov. 2014).

105. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FEES FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTIONS 503B AND 744K OF THE FD&C ACT (Nov. 2014).

106. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR ENTITIES CONSIDERING WHETHER TO REGISTER AS OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (Aug. 2015) [hereinafter *WHETHER TO REGISTER GUIDANCE*].

An outsourcing facility is an entity in one geographic location that compounds sterile drugs, chooses to register as an outsourcing facility, and complies with the requirements of the provision.¹⁰⁷ An outsourcing facility does not need to register as a pharmacy or obtain prescriptions for individual patients.¹⁰⁸ Once registered with FDA, an outsourcing facility is subject to FDA inspection.¹⁰⁹ If an entity decides not to register as an outsourcing facility and does not meet the criteria of a traditional pharmacy, FDA will identify it as a conventional drug manufacturer and subject that entity to the registration requirements and other conditions for such activity under FDCA.¹¹⁰ Section 503B makes it clear that FDA has authority over outsourcing facilities *and* manufacturers, while the state retains authority over traditional pharmacies and traditional compounding defined by Section 503A.¹¹¹

III. STERILE COMPOUNDING STANDARDS

Before the DQSA, regulatory jurisdiction was not the only inconsistent aspect of drug compounding; standards for actual procedures and processing of drug compounding were also inconsistent. There were no national standards for sterile compounding. This section compares the standards that existed pre-DQSA and post-DQSA in order to demonstrate why the current, more stringent standards promulgated by FDA for outsourcing facilities are superior and can lead to more uniform drug production.

A. Pre-DQSA: Lack of Uniform Standards Made It Difficult to Enforce Proper Sterile Compounding, Allowing Pharmacies to Practice Compounding According to Their Arbitrary Discretion

The regulation of compounding hinged on differentiating between compounding from manufacturing by looking at Section 503A of the FDCA or the nine-factored test of the 2002 CPG.¹¹² When it came to the actual act of sterile compounding, the only recognizable standards that existed before the DQSA were the guidelines created by the United States Pharmacopeia (“USP”), titled Chapter 797 (“USP 797”).¹¹³ USP is a non-governmental organization that spe-

107. 21 U.S.C. § 353b(d)(4)(A) (2013).

108. 21 U.S.C. § 353b(d)(4)(B)–(C) (2013).

109. 21 U.S.C. § 353b(b)(4)(A)(i) (2013); *see also* 21 U.S.C. § 374 (2006).

110. WHETHER TO REGISTER GUIDANCE, *supra* note 106, at 4 n.23.

111. *Id.* Section 503A (describing minimal changes); *see supra* note 44.

112. *See supra* Part II.A.1.

113. The first version of USP <797> became official in 2004. It was last revised in 2008. USP finished its latest revisions in 2015, and posted the proposed provisions for public review by January 31, 2016. *Frequently Asked Questions: <797> Pharmaceutical Compounding—Sterile Preparations*, U.S. PHARMACOPEIAL CONVENTION, <http://www.usp.org/frequently-asked-questions/pharmaceutical-compounding-sterile-preparations> (last visited Jan. 1, 2016).

cializes in setting standards for medicine, food ingredients, and dietary supplements.¹¹⁴ It lacks authority to enforce any of its standards, but any government entity at state or federal level can choose to incorporate USP standards into its laws and/or regulations.¹¹⁵

In early 2013, fewer than half the states required pharmacies to comply with USP standards.¹¹⁶ Moreover, there was no uniform standard for education, training, and required experience level of state inspectors, leading to different inspection results of each compounding pharmacy depending on who the inspector was at that time.¹¹⁷ This could have led to discrepancies from pharmacy-to-pharmacy, engendering a dangerous situation since many health facilities relied on the expertise of state inspectors to make sure they were producing sterile and safe drug products in compliance with the governing laws.¹¹⁸ This also posed a problem when pharmacies were distributing across state borders.¹¹⁹ It was not safe to assume that the home state board of pharmacy did an adequate inspection of that particular non-resident pharmacy.¹²⁰ This created inconsistency in compounded drug products across the country.

Massachusetts was one of the states that required compliance with USP 797 for sterile compounding.¹²¹ However, NECC did not follow proper protocols outlined by USP 797, resulting in violations such as improper autoclaving, which compromised the sterility of its products, dirty powder hoods that protected pharmacists from inhaling harmful substances while compounding, and a leaking

114. *About USP*, U.S. PHARMACOPEIAL CONVENTION, <http://www.usp.org/about-usp> (last visited Jan. 1, 2016).

115. Joseph V. Pergolizzi, Jr. et al., *Compounding Pharmacies: Who is in Charge?*, 13 PAIN PRAC. 253, 254 (2013).

116. Besu F. Teshome et al., *How Gaps in Regulation of Compounding Pharmacy Set the Stage for a Multistate Fungal Meningitis Outbreak*, 54 J. AM. PHARMACISTS ASS'N. 441, 444 (2014) (noting that a 2013 survey found only twenty-three states requiring full compliance with USP <797>).

117. PEW CHARITABLE TRUSTS, AM. SOC. HEALTH-SYS. PHARM., AM. HOSPITAL ASS'N, *STERILE COMPOUNDING SUMMIT: SUMMARY OF A STAKEHOLDER MEETING 10, 14* (Feb. 6, 2013) (expressing concern over the inadequate education, training, and experience of state board of pharmacy inspectors that lead to varying compounding practices state-by-state).

118. *See id.* at 14 (noting that hospitals rely on thorough state boards of pharmacy inspections because hospitals “often lack resources or expertise to inspect compounding pharmacies themselves”).

119. GAO COMPOUNDING REPORT, *supra* note 6, at 25–26 (noting that state oversight of pharmacy compounding varied depending on “each state’s regulations and the resources each state devotes to licensing and inspecting its pharmacies,” where some state budgets could not cover the resources needed to have qualified inspectors to inspect pharmacies thoroughly and frequently, compromising the quality of inspections).

120. *See id.* at 25 (recognizing that the “frequency of pharmacy inspections and the qualifications of the pharmacy inspectors vary widely among states, and it is uncertain whether all nonresident pharmacies receive adequate oversight from their home states”).

121. Lloyd K. Jessen, Iowa Board of Pharmacy, Nat’l Assoc. Boards of Pharmacy (NABP) 2012 Triathlon Interactive Executive Officer Forum: Compounding—What Is Manufacturing? What is Compounding? (Nov. 13–14, 2012).

boiler that was forming a pool of water around it.¹²² There were visible black particulates in sealed vials of steroid compounds prepared by NECC.¹²³ Before the DQSA, USP standards were futile because even when states like Massachusetts required USP compliance, no regulatory body was enforcing these standards, allowing pharmacies like NECC to practice compounding according to their own discretion. Unsupervised compounding amplified the precarious back-drop already set in place by unregulated compounding.

B. Post-DQSA: Uniform Standards for Sterile Compounding Will Create Consistently Safe Drug Products

USP 797 was not enough and will never be enough in its current form¹²⁴ for large-scale sterile compounding and that is why the DQSA is necessary.¹²⁵ With its redefined authority from the DQSA, FDA requires outsourcing facilities to comply with Current Good Manufacturing Practice (“CGMP”) standards, which are overall more comprehensive and rigorous than USP 797.¹²⁶ This section goes into greater detail about specific parts of FDA guidance regarding CGMP requirements to demonstrate how CGMPs are more appropriate than USP 797 for large-scale sterile compounding.

1. CGMP is the Minimum Standard Outsourcing Facilities Should Use to Develop Their Best Practices

In its July 2014 interim draft guidance, FDA established minimum standards for sterile compounding done by outsourcing facilities based on CGMPs.¹²⁷ Looking at the guidance in its totality, the purpose of adapting CGMPs for outsourcing facilities seems to be creating an infallible and almost innate system

122. COMMONWEALTH OF MA. EXEC. OFFICE OF HEALTH AND HUMAN SERV. DEP’T OF PUBLIC HEALTH, NEW ENGLAND COMPOUNDING CENTER (NECC) PRELIMINARY INVESTIGATION FINDINGS, at 4–5 (2012).

123. *Id.* at 4.

124. USP’s proposed revisions to Chapter 797 was published for public commenting on November 2, 2015 and closed on January 31, 2016. One of the major changes recognizes that all sterile compounds should be carefully prepared because “no sterile compounding is inherently ‘low risk.’” *General Chapter <797> Pharmaceutical Compounding—Sterile Preparations Notice of Intent to Revise*, USP (Sept. 25, 2015), <http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision>.

125. ERIC S. KASTANGO & KATHERINE H. DOUGLASS, CLINICAL IQ LLC, QUALITY STANDARDS FOR LARGE SCALE STERILE COMPOUNDING FACILITIES 11 (2014).

126. *See infra* Part III.B.1.

127. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CURRENT GOOD MANUFACTURING PRACTICE—INTERIM GUIDANCE FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTIONS 503B OF THE FD&C ACT (Jul. 2014) [hereinafter CGMP GUIDANCE].

that can be used on a routine basis in order to guarantee sterility and high-quality products.¹²⁸

CGMPs were created to serve as a minimum set of standards for implementing quality systems and risk management to “assure[] the identity, strength, quality, and purity of drug products by requiring manufacturers of pharmaceuticals adequately control their manufacturing operations.”¹²⁹ CGMPs have been adopted internationally and represent a way to standardize manufacturing of so that each drug product put on the market by any manufacturing company is reliably safe and effective for consumer use.¹³⁰ Unlike the manufacturing of commercial drugs, compounding never had a uniform national standard before the DQSA.¹³¹ As mentioned before, some states required USP 797 compliance, but state-level enforcement of these standards was not always reliable.¹³²

Moreover, USP 797 has always been meant for traditional small-scale compounding.¹³³ When it comes to large-scale compounding where one batch may affect multiple patients, the production process needs tighter limits and surveillance methods in order to minimize the risk of contamination.¹³⁴ Thus, the intention of applying CGMPs to outsourcing facility compounding is similar to manufacturing: to establish comprehensive and rigorous standards for the production of safe and sterile compounded drugs suitable for widespread use.

FDA’s interim guidance for CGMP requirements (“cCGMPs”) is specifically customized for sterile compounding prepared by outsourcing facilities.¹³⁵ The main purpose of the interim guidance is the “assurance of sterile drug products and the safety of compounded drug products”¹³⁶ The goal for sterile and safe drug production is the same for USP 797, but it differs from cCGMPs in terms of what should be emphasized when a compounding facility develops

128. KASTANGO & DOUGLASS, *supra* note 125, at 11 (relating large scale compounding to manufacturing where “[s]ystematic evaluation and elimination of variability within a manufacturing process is a cornerstone of predictable quality outcomes”).

129. *Facts About Current Good Manufacturing Practices (CGMPs)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm> (last updated Jan. 6, 2015).

130. *Id.*

131. *See supra* Part III.A.

132. *See supra* notes 116–20 and accompanying text.

133. This may change when the revised USP is released. *See infra* note 125.

134. KASTANGO & DOUGLASS, *supra* note 125, at 10 (noting the importance of “robust quality assurance practices, such as those described under CGMPs” because the resulting drug products from large-scale compounding “reach hundreds of patients across the country”).

135. CGMP GUIDANCE, *supra* note 127, at 2 (“This interim guidance reflects FDA’s intent to recognize the differences between compounding outsourcing facilities and conventional drug manufacturers, and to tailor CGMP requirements to the nature of the specific compounding operations conducted by outsourcing facilities . . .”).

136. *Id.* at 3.

its best practices. The following subsections describe some key differences between USP 797 and cCGMPs.

a. Identity and Quality of Components Best Practices

The identity and quality of ingredients directly affects the integrity of a sterile compounded drug. It is essential to start with proper components¹³⁷ because if the components are compromised from the beginning, then the process may be delayed or result in a product that is not safe for patient consumption. One of the more prominent differences between cCGMPs and USP 797 is the standard of ensuring identity, strength, quality, and purity for every drug production. USP 797 has no specific guidance on confirming the identity and quality of components,¹³⁸ while cCGMPs detail and emphasize the importance of having control over the source and quality of all components, including non-sterile materials or other ingredients used to compound sterile drugs.¹³⁹

Regarding the quality of ingredients used in a compound, USP 797 generally states: “Compounding personnel ascertain that ingredients for [compounded sterile preparations] are of the correct identity and appropriate quality using the following information: vendor labels, labeling, certificates of analysis, direct chemical analysis, and knowledge of compounding facility storage conditions.”¹⁴⁰ In contrast, cCGMPs expand on each of those criteria and more.

First, specifications of the components of a particular compound must be predetermined.¹⁴¹ These specifications equate to the finished compounded product’s quality, which include identity, strength, purity, particle size, sterility, and bacterial endotoxin level.¹⁴² Then, each batch of components needs to be tested and verified for its alleged identity.¹⁴³ However, FDA will not enforce such testing if before use, the component is an approved finished drug product obtained directly from a FDA-registered manufacturer, labeled appropriately, verified as compliant with the required specifications, and shipped in an intact package with a valid receipt.¹⁴⁴

Testing can be waived if there is a Certificate of Analysis (“COA”) from the supplier.¹⁴⁵ The problem with a COA is that if the supplier only repackages

137. Components consist of bulk active ingredients, excipients, and other ingredients, but not finished drugs. *Id.* at 9 n.12.

138. KASTANGO & DOUGLASS, *supra* note 125, at 19.

139. CGMP GUIDANCE, *supra* note 127, at 8–9.

140. U.S. PHARMACOPEIA, 2012 USP 35/NF 30: USP-NF GENERAL CHAPTER <797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS 20 (2011) [hereinafter USP CHAPTER 797]

141. CGMP GUIDANCE, *supra* note 127, at 8.

142. *Id.*

143. *Id.*

144. All of these conditions must be met to be exempt from FDA inspection. *Id.* at 8–9.

145. *Id.* at 9.

components, they are not required to do specific qualitative testing and/or evaluation of their components.¹⁴⁶ Thus, a COA may not be a true testament of a component's quality. To accommodate for this discrepancy, the guidance states that a COA is acceptable only when it comes from a supplier whose reliability has been proven at appropriate intervals¹⁴⁷ and at least one identity test has confirmed the component.¹⁴⁸ However, recognizing the potential redundancy of this requirement, FDA requested public comments on alternatives "that would enable an outsourcing facility to have confidence in the quality of incoming components without periodic laboratory testing following initial qualification testing to confirm the information in the supplier's [COA]."¹⁴⁹

To gauge the opinions of its relevant constituents, FDA suggested a specific alternative within its interim guidance. The alternative consists of differentiating between a supplier who is the original manufacturer of a component and a supplier who is not.¹⁵⁰ Under this approach, a supplier who is not the original manufacturer would be required to submit a drug master file ("DMF") that describes in detail the qualitative tests and assurances of the component, have the DMF approved by FDA, commit to updating the DMF accordingly, provide a copy of the DMF to the purchasing outsourcing facility, and give notice of any changes in the component's quality to the purchasers.¹⁵¹ In the event that an outsourcing facility wants to use DMFs in lieu of testing requirements, it must notify FDA of those intentions.¹⁵²

Under FDA's approach to reduce superfluous quality testing of components, non-manufacturer suppliers will indirectly be held to higher and stricter standards of quality assurance.¹⁵³ This will allow outsourcing facilities to be confident when purchasing components. However, it may not be so well-received by suppliers who may need to configure new systems and best practices of their own in order to become reliable sources of components. This alternative can have several consequences, including filtering out suppliers who cannot afford the resources necessary to comply with DMF requirements, leaving only manufacturer suppliers to sell components. Assuming a steady demand of compounded products with fewer suppliers, prices of components can increase and in effect increase the price of the finished compounded product.

146. KASTANGO & DOUGLASS, *supra* note 125, at 19.

147. For example, a supplier demonstrates its reliability through appropriate procedures and tests at least annually for active ingredients and every two years for other components. CGMP GUIDANCE, *supra* note 127, at 9.

148. *Id.*

149. *Id.* at 10.

150. *Id.* at 10–11.

151. *Id.* at 11.

152. *Id.* at 10.

153. See *supra* text accompanying note 151.

b. Production and Process Best Practices

Personnel education and training is the most important, but limiting factor for sterile processing and production of compounded drugs. Although USP 797 updated their standards in 2008 placing more emphasis on personnel training and evaluation,¹⁵⁴ it “lack[s] the qualitative and quantitative specificity and rigor needed for large-scale compounding operations.”¹⁵⁵ cCGMPs prove to be better standards for outsourcing facilities because these expect a higher level of personnel training, which in effect will help to produce higher quality drug production.

Both USP 797 and cCGMPs recommend testing personnel for proper technique and behavior with a media fill simulation.¹⁵⁶ USP 797 outlines a media fill simulation in a non-specific way: “Media-fill tests shall represent the most challenging or stressful conditions actually encountered by personnel being evaluated when they prepare . . . [compounded sterile preparations].”¹⁵⁷ cCGMPs describe “media fill studies” to “closely simulate aseptic manufacturing operations incorporating, as appropriate, *worst-case* activities and conditions that provide a challenge to aseptic operations.”¹⁵⁸ cGMPs go on to list several challenges that should be addressed in the simulation, such as the number of personnel and activities, shift or garbing changes, equipment assembly and manipulation issues, and other processing issues.¹⁵⁹ Moreover, each individual needs to pass at least three successive simulations in order to be qualified to conduct aseptic operations.¹⁶⁰

cCGMPs go beyond USP 797’s general recommendation that personnel should be trained “conscientiously and skillfully” and “maintain a formal education, training, and competency assessment program that encompasses all the functions and tasks addressed.”¹⁶¹ cCGMPs view personnel as active participants of a compounding facility. The interim guidance suggests a systematic approach that consists of routine (daily or every shift change) monitoring of gloves and gowns during operations, establishing limits based on the contamination risk of a product, and investigating results that are abnormal, inconsistent, adverse, or in excess of the prescribed limits.¹⁶²

154. Cheryl A. Thompson, *USP Releases Revision of Chapter on Sterile Compounding*, 65 AM. J. HEALTH-SYST. PHARMACY 104, 104 (2008).

155. KASTANGO & DOUGLASS, *supra* note 125, at 23 (comparing the minimum garbing requirements between USP 797 and CGMPs to note that USP 797 “does not provide any qualitative guidance on this topic,” whereas CGMPs specifically state that personnel “may not have any exposed skin” in aseptic processing areas and “must be vigilant about how they move and work within the critical filling zones”).

156. USP CHAPTER 797, *supra* note 140, at 18; CGMP GUIDANCE, *supra* note 127, at 14.

157. USP CHAPTER 797, *supra* note 140, at 18.

158. CGMP GUIDANCE, *supra* note 127, at 14 (emphasis added).

159. *Id.*

160. *Id.* at 12.

161. USP CHAPTER 797, *supra* note 140, at 7, 24.

162. CGMP GUIDANCE, *supra* note 127, at 6–7.

This last criterion of investigating abnormalities seems to emphasize that personnel need to be active and alert at all times. Even the media fill studies are designed around “worst-case scenarios” and not just “challenging or stressful conditions” to evaluate an individual’s awareness and attentiveness.¹⁶³ Personnel should not only be able to consistently produce sterile compounds, but also consistently detect deviations from the prescribed best practices and resolve them in a timely fashion.¹⁶⁴ Betterment can only be processed and performed by people, not automated machinery. Calling for personnel who are well trained, skillful, and mindful will make these best practices successful and enduring.

c. Release Testing Best Practices

Release testing is another area where USP 797 and cCGMPs diverge. Before a finished sterile compounded product is released for distribution, it needs to be tested once more to confirm at a minimum: its identity, strength, stability, and the presence of visible particles and bacterial endotoxins.¹⁶⁵ Of the criteria for release testing, the protocol for stability testing is one of the major differences between USP 797 and cCGMPs.

Stability testing is performed to determine and assign the appropriate expiration date or beyond-use date (“BUD”) of the final product.¹⁶⁶ According to USP 797, “BUDs . . . are usually assigned on the basis of professional experience . . . BUDs for [compounded sterile preparations] are rarely based on preparation-specific chemical assay results” like those used for commercially manufactured drug products.¹⁶⁷ Instead, USP 797 prescribes BUDs according to the level of contamination risk of a compound: immediate use, low-risk, medium-risk, and high-risk.¹⁶⁸ Immediate use is a product that needs to be used within one hour after the product has begun compounding and is exempt from BUD requirements in USP 797 due to its urgent need.¹⁶⁹ High-risk includes using non-sterile components to compound a sterile compound or putting sterile products into a non-sterile container.¹⁷⁰ High-risk products have a BUD of 24 hours at room temperature, three days in the refrigerator, and 45 days in the freezer.¹⁷¹ All other sterile products fall along the spectrum according to the professional judgment of personnel and/or the outsourcing facility.¹⁷²

163. See *supra* text accompanying notes 157–158.

164. See *supra* text accompanying notes 157–164.

165. CGMP GUIDANCE, *supra* note 127, at 14–15, 18.

166. *Id.* at 18.

167. USP CHAPTER 797, *supra* note 140, at 22.

168. *Id.* at 4, 7.

169. Urgent situations include “cardiopulmonary resuscitation, emergency room treatment, [and] preparation of diagnostic agents.” *Id.* at 7.

170. *Id.* at 6.

171. *Id.*

172. *Id.* at 4–6.

cCGMPs leave no room for professional discretion in determining BUDs. If a final product is terminally sterilized¹⁷³ without release testing, the product must have a BUD of 14 days or less.¹⁷⁴ If the final product was aseptically processed¹⁷⁵ without release testing, the product can only have a BUD of twenty-four hours at USP controlled room temperature, three days refrigerated, and/or forty-five days in a solid frozen state.¹⁷⁶ This BUD also applies to batches of ten or less dosage units.¹⁷⁷ If the final product completes release testing, the BUD can be extended up to fourteen days at USP controlled room temperature or refrigerated or forty-five days in a solid frozen state.¹⁷⁸ Completing release testing affords the longest BUD.¹⁷⁹ Compared to USP 797, FDA recommends simplified but stricter parameters for BUD assignment.¹⁸⁰

The more stringent protocol may be burdensome for outsourcing facilities that compound smaller batches containing ten or fewer units. This becomes even more controversial when it comes to compounding a prescription-based order. If two identical low-risk compounds¹⁸¹ pursuant to an individual prescription are produced—one by an outsourcing facility following cCGMPs and the other by a traditional pharmacy following USP 797—the BUD for the compound made by the outsourcing facility would be twenty-four hours at room temperature and the BUD for the compound made by the traditional pharmacy would be forty-eight hours at room temperature.¹⁸² Outsourcing facilities may find it unfair that they must abide by stricter limits, while traditional pharmacies under Section 503A are able to compound the same types of prescription-based orders without such constraints.¹⁸³ FDA will need to address how it will reconcile these differences

173. Terminal sterilization is the process of sterilizing the finished drug product in its sealed container “under high-quality environmental conditions” such as heat or irradiation. In contrast, an aseptic process consists of sterilizing the drug product, container, and closure separately then assembled together. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: STERILE DRUG PRODUCTS PRODUCED BY ASEPTIC PROCESSING—CURRENT GOOD MANUFACTURING PRACTICE 2 (Sept. 2004).

174. CGMP GUIDANCE, *supra* note 127, at 18.

175. *Id.*

176. *Id.* at 18.

177. *Id.* at 15. “One dosage unit is the amount of drug in a labeled dose, e.g., one tablet or one syringe.” *Id.* at 15, n.14.

178. The BUD begins after completion of release testing. *Id.* at 18.

179. *Id.*

180. See *supra* text accompanying notes 168–171, 174–178.

181. An example of a low-risk compound according to USP standards would be the reconstitution (mixing a powdered drug with liquid) of an antibiotic then injecting the reconstituted drug into an IV bag. USP CHAPTER 797, *supra* note 140, at 5.

182. Compare CGMP GUIDANCE, *supra* note 127, at 18 with USP CHAPTER 797, *supra* note 140, at 5.

183. Traditional compounding under Section 503A are not subject to CGMPs. 21 U.S.C. § 353a(a) (2013).

and clarify how it will differentiate outsourcing facilities from traditional pharmacies as to not undermine their purpose and limit their operations.¹⁸⁴

2. *Mandatory Adverse Event Reporting Places Accountability on Outsourcing Facilities*

Post-market safety surveillance of any type of drug is crucial to continued protection of consumer health. Manufacturers are required to send safety reports to FDA through MedWatch.¹⁸⁵ Individual consumers and health care providers can voluntarily report any safety issues to FDA as well.¹⁸⁶ Before the DQSA, FDA only knew about adverse events related to compounded products if and when these events were voluntarily reported.¹⁸⁷ With the passage of the DQSA, adverse event reporting (“AER”) now also applies to outsourcing facilities, placing accountability and liability on their productions.¹⁸⁸

An “adverse drug experience” is an undesirable occurrence “associated with the use of [a] compounded . . . product” in a health care setting, including overdose, drug abuse, drug withdrawal, or when the drug does not work as expected.¹⁸⁹ A “serious adverse drug experience” is a more heightened situation in which the drug results in a life-threatening event that may require hospitalization or results in death.¹⁹⁰ An “unexpected adverse drug experience” is an event not

184. FDA recognizes that a traditional pharmacy and an outsourcing facility may have overlapping operations. However, FDA adamantly states that any compound produced in an outsourcing facility must be made under CGMP requirements regardless of whether the same compound can be made under USP conditions in a traditional pharmacy. Traditional pharmacy under Section 503A and outsourcing facility under Section 503B must be distinctly separate to “prevent commingling of compounding activities” and protect public health by “ensur[ing] that those obtaining the drugs will know the standards under which they were compounded.” U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: FACILITY DEFINITION UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 4–5 (Apr. 2016) [hereinafter FACILITY DEFINITION GUIDANCE].

185. *Questions and Answers on FDA Adverse Event Reporting System (FAERS)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Mar. 14, 2016); see also *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/MedWatch/default.htm> (last updated Apr. 20, 2016); 21 C.F.R. §§ 314.80(c), 803.30, 803.50 (2015).

186. *Questions and Answers on FDA Adverse Event Reporting System (FAERS)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Mar. 14, 2016).

187. GAO COMPOUNDING REPORT, *supra* note 6, at 16.

188. 21 U.S.C. § 353b(b)(5).

189. 21 C.F.R. § 310.305(b) (2015).

190. *Id.* Specifically, any adverse drug experience refers to an event that occurs at any dose and results in any of the following: life-threatening experience or death, hospitalization, significant disability or incapacity, or congenital anomaly or birth defect. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ADVERSE EVENT REPORTING FOR OUTSOURCING FACILITIES UNDER SECTIONS 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 4 (Oct. 2015) [hereinafter AER GUIDANCE].

found on the labeling of the final product – a rare or never before observed experience associated with the drug.¹⁹¹ Outsourcing facilities are required to report all unexpected adverse experiences and are strongly encouraged to report all serious adverse experiences.¹⁹² Reports must be made within fifteen days of first receiving the information of the adverse event and must be followed by prompt investigation and a follow-up report, if necessary, within fifteen days of receiving any new information.¹⁹³ All records and reports need to be kept for ten years, readily accessible to FDA during inspection or when asked.¹⁹⁴

The standard for adverse drug experience reporting is now the same for outsourcing facilities and manufacturers and is under the direct supervision of FDA.¹⁹⁵ This should compel outsourcing facilities to develop best practices that include regular reevaluation of their procedures for sterile compounding and integration of a recalling system. Accountability is now fundamental to becoming an outsourcing facility.

IV. OTHER ISSUES AND IMPLICATIONS

The DQSA is not perfect; no law ever is. The DQSA's success will depend on how FDA takes possession of its unmistakable authority over outsourcing facilities. In its nascence, there are several issues that need to be addressed. One issue previously discussed is the need for FDA to reconcile the differences of regulating traditional pharmacies and outsourcing facilities, especially when both entities overlap in their operations.¹⁹⁶ This part of the note will explore other prominent issues brought to light as FDA is implementing the DQSA: how FDA will ultimately tailor CGMP requirements to outsourcing facilities without disadvantaging manufacturers' CGMP requirements and how FDA will cooperate with states in order to facilitate the harmonious coexistence of the DQSA and local laws. Lastly, all issues and criticisms aside, this part will look at how outsourcing facilities have the potential to alleviate critical drug shortages.

A. *CGMP Compliance: Large-Scale Compounding vs. Manufacturing*

There is criticism that a new class of drug distributors is unnecessary for better regulation of large-scale drug compounding because outsourcing facilities are basically bound to the same CGMP requirements as manufacturers.¹⁹⁷ Critics argue that outsourcing facilities should not be given a more lenient version of

191. 21 C.F.R. § 310.305(b) (2015).

192. AER GUIDANCE, *supra* note 190, at 5.

193. 21 U.S.C. § 310.305(c) (2015).

194. AER GUIDANCE, *supra* note 190, at 10.

195. *See supra* text accompanying notes 185, 188.

196. *See supra* Part III.B.1.c.

197. *See supra* Part III.B.

CGMPs just because they are “compounding” and not “manufacturing,” especially since both processes result in the creation of a drug.¹⁹⁸ However, this is only partially true. While both compounding and manufacturing result in a “drug,” the two processes each have a different purpose¹⁹⁹—a distinction FDA should consider when finalizing its CGMP guidance for outsourcing facilities.

Pharmaceutical Research and Manufacturers of America (“PhRMA”), an organization that represents pharmaceutical manufacturers, is one of the opponents of the creation of a third class of drug distributors.²⁰⁰ PhRMA argues that both compounders and manufacturers should be held to the same high standards of drug production.²⁰¹ When the DQSA directs outsourcing facilities to comply with CGMP requirements, Congress clearly intended compounds to be regulated like manufactured drugs; having a separate category of drug distributors is redundant.²⁰²

Public Citizen’s Health Research Group (“Public Citizen”), a non-profit consumer rights advocacy group, agrees that a third category only undermines the strict legal standards that have been in place for conventional manufacturers for many years.²⁰³ Outsourcing facilities will have a lenient version of federal requirements (i.e. exemption from pre-market approval requirements) when both compounds and manufactured drug products pose similar risks of safety and efficacy.²⁰⁴ Public Citizen worries that this second-tier manufacturing will only stimulate the growth of substandard drug manufacturing.²⁰⁵ Instead of having this in-between category of drug distributors, Public Citizen agrees with PhRMA

198. *Reforming the Drug Compounding Regulatory Framework: Hearing Before the Subcomm. On Health of the H. Comm. on Energy and Commerce*, 113th Cong. 82 (2013) [hereinafter *Reforming Drug Compounding Regulation 2013 House Hearing*] (statement of Jeffrey K. Francer, Assistant General Counsel, Pharmaceutical Research & Manufacturers of America) (“Large-scale, commercial manufacturing of prescription medicines . . . should be governed by the same high standards as biopharmaceutical manufacturing—whether the producer is designated as a ‘pharmacy’ or as a ‘manufacturer.’”); see also *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of David Sterrett, Health Care Counsel, Public Citizen’s Health Research Group), *supra* note 198, at 154 (“All drug manufacturers [commercial and compounding] should be held to the same standards.”).

199. See *infra* text accompanying notes 215–216.

200. See *infra* text accompanying notes 215–216.

201. *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of Jeffrey K. Francer, Assistant General Counsel, Pharmaceutical Research & Manufacturers of America), *supra* note 198, at 82 (“The manufacturing of medicines, whether by manufacturers or pharmacies, should be regulated in a consistent, risk-based manner.”).

202. See *id.* at 82–83 (“Congress intended for large-scale, commercial production of medicines to be regulated by FDA applying cGMP standards”).

203. Mari Serebrov, *PhRMA: Compounders Just Drugmakers by Another Name*, *BIO WORLD TODAY* (July 17, 2013), <http://www.bioworld.com/content/phrma-compounders-just-drugmakers-another-name-0>.

204. See *id.* (concurring that “[m]edicines that present similar risks should be regulated similarly”).

205. *Id.*

that this new category of an outsourcing facility is unnecessary and could result in further complications in federal and state regulation.²⁰⁶

When it comes to the sterility and safety of drug products, redundancy does not seem to be an issue for FDA. FDA responded to PhRMA by giving the example of hospitals that have relied on compounding pharmacies for their supply of sterile products that were previously made in-house.²⁰⁷ Compounding is a crucial way to efficiently meet the specific health care needs of certain patients.²⁰⁸ If compounding was subject to the same criteria as manufacturing a “new drug,” then it would be too time-consuming and defeat the purpose of providing the needed drug quickly. Whereas manufacturing does not have an imminent patient consumer, compounding (traditional or non-traditional) typically has a specific patient population waiting for or in need of the specific compound.²⁰⁹

For FDA, the more relevant distinction seems to be between traditional and non-traditional compounding rather than between non-traditional compounding and manufacturing, as seen in Congressional testimonies leading up to the drafting of the DQSA.²¹⁰ It is important to separate traditional individual-based com-

206. *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of Jeffrey K. Francer, Assistant General Counsel, Pharmaceutical Research & Manufacturers of America), *supra* note 198, at 80 (arguing that a new category of compounders is unnecessary because it would “result in regulatory confusion (both federal and state) and the application of different regulatory standards (and patient protections) for similar types of manufacturing”).

207. *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of Janet Woodcock, Director Center for Drug Evaluation and Research, U.S. Food & Drug Admin.), *supra* note 198, at 27–8 (recognizing that outsourcers provide a valuable service to hospitals that cannot compound in-house, such as “specialized dilutions of FDA-approved products” of surgery aesthetics); *see also* Charles E. Myers, *History of Sterile Compounding in U.S. Hospitals: Learning From the Tragic Lessons of The Past*, 70 AM. J. HEALTH-SYST. PHARM. 1414, 1417 (2013) (recognizing that there were many factors that contributed to hospitals outsourcing and in the 1980s, one of those reasons was the increased need for home infusion services upon a patient’s discharge while hospitals were unable to physically expand to meet the demands for sterile compounding, so patients were referred to compounding pharmacies for home infusion services).

208. *See infra* Part IV.C.

209. *See supra* note 30; *see also* Charlotte Matheny & Caren McHenry Martin, *Compounding Pharmacy: Old Methods Finding a New Niche*, 25 CONSULTANT PHARMACIST 357, 360 (2010) (describing specific patient populations who benefit from compounded drug products, such as pediatrics, geriatrics, those who cannot swallow, those with allergies to certain ingredients, and those who may need specific formulations unavailable commercially).

210. *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. On Oversight and Investigations of the H. Comm. on Energy and Commerce*, 112th Cong. 47 (2012) (statement of Margaret A. Hamburg, Commissioner of Food and Drugs, U.S. Food & Drug Administration) (recommending distinctly that “the statute recognize two categories of compounding: traditional and non-traditional”); *see also Meningitis Outbreak 2013 House Hearing*, *supra* note 71, at 22 (reiterating that there needs to be a clear distinction between traditional and non-traditional compounding because non-traditional compounding involves higher risks and thus should be regulated by FDA whereas traditional compounding has lower risks and thus can remain within State oversight); *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of Janet Woodcock, Director Center for Drug Evaluation and Research, U.S. Food & Drug Admin.), *supra* note 198, at 34–35 (emphasizing that the main issue from

pounding from non-traditional large-scale compounding because the latter is associated with higher risks since its products have a higher chance of being exposed to more people.²¹¹ Higher risks necessitate greater oversight that includes following CGMP standards like conventional drug manufacturers.²¹² In this sense, FDA seems to agree with PhRMA in that there is no significant difference between large-scale compounding and conventional manufacturing because both produce high-risk drug products traversing interstate commerce and should be subjected to stricter regulation.²¹³

Thus, an outsourcing facility *should* be regulated like a manufacturer because it should be held to the same high standards and best practices as a manufacturer. However, there is a major difference—outsourcing facilities do not produce new active ingredients; they work with already existing ingredients to compound them in a way that is needed or preferred for a specific patient or group of patients.²¹⁴ Manufacturers formulate completely new drugs or generic versions from scratch, subject to the standards of safe and *effective* products.²¹⁵ Nowhere in the DQSA or FDA guidance documents does it state that a compounded product must demonstrate its effectiveness in terms of how well it works for the intended indication. If the concern of a drug product is its effectiveness, then that product falls under manufacturing territory.

Outsourcing facilities should not be subject to pre-market requirements such as conducting clinical studies to prove a drug's effectiveness in treating a certain disease or condition. FDA needs to create a final guidance on CGMPs for outsourcing facilities considering and differentiating each category of drug distributors by its individual purpose. Manufacturers create commercial drugs from scratch, outsourcing facilities customize compounded drugs with existing ingredients, and traditional pharmacies dispense manufactured drugs and/or compound for patient-specific orders. CGMPs for outsourcing facilities may be outlined more leniently compared to manufacturers, but FDA should not compromise on the rigor that CGMPs emphasize for drug process and production. The interim guidance already manifests that FDA will preserve this stringent approach to outsourcing facilities.²¹⁶

the beginning has been about “establish[ing] a bright line between State and Federal jurisdiction,” which separates small-scale individual-based from large-scale traversing interstate commerce compounding).

211. See *supra* text accompanying note 93.

212. *Reforming Drug Compounding Regulation 2013 House Hearing* (statement of Janet Woodcock, Director Center for Drug Evaluation and Research, U.S. Food & Drug Admin.), *supra* note 198, at 35 (recognizing that the problem with large-scale compounding is that there are no standardized practices for aseptic compounding, such as CGMPs for conventional manufacturers).

213. See *supra* notes 198, 202 and accompanying text.

214. See *supra* note 6.

215. See *supra* note 25 and accompanying text.

216. See *supra* text accompanying note 127.

B. Preemption Issues: State and Federal Governments Need to Collaborate Efficiently to Not Create Another Ineffective Statute

An entity can voluntarily choose to register with FDA as an outsourcing facility and become subject to FDA regulation such as routine inspection, compliance with cCGMPs, and reporting of adverse events.²¹⁷ That same entity may need an additional license or registration to operate within the state of its residence.²¹⁸ Furthermore, a state may only mandate USP 797 as the minimum sterile compounding standards.²¹⁹ The fact that state and federal laws do not mirror each other may demonstrate complications and reignite jurisdictional issues of whether the state or FDA has oversight over a particular compounding entity. If the state and FDA do not cooperate effectively, the DQSA may end up being a futile attempt to smooth out the regulatory landscape.

Unlike Title II of the DQSA,²²⁰ Title I does not explicitly state that it preempts all state standards and policies pertaining to large-scale compounding.²²¹ FDA does not clarify the issue either, but in its draft guidance on repackaging the agency does differentiate between a state-licensed pharmacy or federal facility and an outsourcing facility by establishing different requirements.²²² Whether FDA will keep these distinctions in other areas of DQSA implementation is unclear.²²³

As for acknowledging the new category of drug distributors,²²⁴ as of February 2016, only thirteen states require that an entity conducting sterile compounding without a patient-specific prescription be registered with FDA as an outsourcing facility.²²⁵ Some states have already adopted the new category of an

217. 21 U.S.C. § 353b(b) (2013).

218. See *infra* note 227 and accompanying text.

219. See *supra* note 113 and accompanying text.

220. The Drug Supply Chain Security Act, Pub. L. No. 113-54, 127 Stat. 599 (2013) (codified at 21 U.S.C. § 360eee (2013)).

221. 21 U.S.C. § 360eee-4(b)(1) (2013).

222. For example, if a sterile drug product is repackaged in a state-licensed pharmacy or a federal facility, the repackaged product should have a BUD of at most thirty hours if stored at a USP controlled room temperature, at most 9 days if stored in a refrigerator, or at most forty-five days if stored in a solid frozen state. In contrast, if the sterile product is repackaged by an outsourcing facility, the product needs to first pass CGMP sterility testing before it can be assigned a specific BUD. U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: REPACKAGING OF CERTAIN HUMAN DRUG PRODUCTS BY PHARMACIES AND OUTSOURCING FACILITIES 6–8 (Feb. 2015) [hereinafter REPACKAGING GUIDANCE].

223. *But see supra* note 184 (emphasizing the importance of separating traditional pharmacies, following most likely USP standards, from outsourcing facilities that must follow CGMP requirements).

224. For the purposes of this paper, there are three main “drug distributors”: 503A traditional pharmacy, 503B outsourcing facility, and manufacturer. An outsourcing facility is the new category of drug distributors created by the DQSA.

225. PEW CHARITABLE TRUSTS, NATIONAL ASSESSMENT OF STATE OVERSIGHT OF STERILE DRUG COMPOUNDING 17 (2016) [hereinafter PEW REPORT].

outsourcing facility, requiring a separate state license and/or registration.²²⁶ Some states require that regardless of being federally registered as an outsourcing facility, entities must register with the state as a pharmacy, manufacturer, or wholesaler, or both a manufacturer and a wholesaler.²²⁷ Several states remain undecided.²²⁸ This hodgepodge of requirements for state licensure and registration runs the risk of creating more confusion in a post-DQSA landscape of compounding. This can prove challenging especially when compounds cross state borders: if one state requires an outsourcing facility to also be registered as a pharmacy and another state does not, an unregistered outsourcing facility that wants to do business in both states may be in a complicated (and perhaps expensive) situation.²²⁹

Although FDA has adapted CGMPs for outsourcing facilities, the fact that the repackaging guidance applies different standards to outsourcing facilities from state-licensed pharmacies manifests arbitrary discrepancy. The repackaging guidance specifically states that a state-licensed pharmacy should comply with USP 797 when repackaging a drug.²³⁰ However, the same guidance states that if the drug is repackaged in an outsourcing facility, it must be done in accordance with CGMP requirements.²³¹ Similar to the issue of an outsourcing facility and a traditional pharmacy compounding prescription-based products,²³² FDA needs to fully explain why outsourcing facilities are held to a higher standard besides the fact that the DQSA now requires outsourcing facilities to comply with CGMPs.²³³

As illustrated by the pre-DQSA circuit split, complications turn into confusion and chaos when there are different standards being applied across the country. Under the Supremacy Clause, the DQSA preempts all state laws, rules, and

226. These states are California, Delaware, Florida Idaho, Mississippi, New York, and Tennessee. *id.* at 15.

227. *Id.* at 15, 17. Title I of the DQSA states, “[a]n outsourcing facility is not required to be a licensed pharmacy,” which does not preclude an outsourcing facility from being a State-licensed pharmacy. 21 U.S.C. § 353b(d)(4)(B) (2013). Moreover, Title I states that an outsourcing facility cannot sell its products to a wholesaler. 21 U.S.C. § 353b(a)(8) (2013).

228. PEW REPORT, *supra* note 225, at 17.

229. *Id.* at 15–16.

230. REPACKAGING GUIDANCE, *supra* note 222, at 7–8.

231. *Id.* at 8.

232. *See supra* text accompanying notes 165–168.

233. Although the facility definition draft guidance recognizes operational overlaps and stresses the importance of keeping compounding standards for traditional pharmacies and outsourcing facilities separate, the guidance does not fully explain why different standards must apply. The guidance only explains why a traditional pharmacy and an outsourcing facility should not operate at the same location or address due to the risk of sharing and mixing instruments, methods, and supplies that will make it “difficult to ensure that all of the products were made under the correct standards.” FACILITY DEFINITION GUIDANCE, *supra* note 184, at 4.

regulations regarding the existence and operation of an outsourcing facility.²³⁴ Therefore, all states must require an entity compounding sterile drug products in large quantities to register as an outsourcing facility with FDA and be subject to FDA inspections. In order to do so, FDA first needs to form a strong partnership with the states so that each state recognizes outsourcing facilities in the same manner as the DQSA. Second, FDA and the states need to define what it means to become an outsourcing facility in terms of licensure and how this will affect shipping compounds across state borders. Third, FDA needs to address the discrepancies that exist when outsourcing facilities and traditional pharmacies overlap in operations and are held to different standards.²³⁵ Finally, FDA and the states need to define how their partnership will stay in close communication and operate together to enforce effective regulation. FDA and state authorities need to work collaboratively and efficiently to make sure that the DQSA does not create another complicated regulatory landscape.

C. Public Health Remedy: Outsourcing Facilities Have the Potential to Alleviate Drug Shortages

Drug shortages are multifaceted issues that impact patient care and difficult to resolve completely.²³⁶ The DQSA has the potential to help alleviate this problem by permitting outsourcing facilities to compound any drug that is on FDA's drug shortage list.²³⁷ Outsourcing facilities can take advantage of this niche because they follow strict CGMP guidelines to produce high quality sterile products like manufacturers, but provide the products in quicker made-to-order fashion like a traditional pharmacy.²³⁸ However, the success of outsourcing facilities

234. U.S. CONST. art. VI, § 2 ("This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land . . .").

235. See *supra* note 233.

236. List of current drug shortages according to FDA can be found at: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>. List of current drug shortages according to ASHP can be found at: <http://www.ashp.org/menu/DrugShortages/CurrentShortages>. The two lists may have discrepancies and differences because the intent and audience for each list is different. While FDA's list is for the general public and compiled by reports mainly from the drug manufacturers, ASHP's list is for healthcare practitioners and compiled by reports from anyone (e.g. practitioners, patients, manufacturers). FDA defines a drug to be in shortage when the supply from all providers does not meet the demand. FDA has a general public health perspective. On the other hand, ASHP considers a drug to be in shortage until every version by every manufacturer has returned to supply the product. This is useful for a practitioner looking to see why all of a sudden a certain type of drug is no longer available and what other manufacturer(s) may be able to provide it. FOOD AND DRUG ADMIN., AM. SOC'Y HEALTH-SYS. PHARM., & U. UTAH DRUG INFO. SERVICE, CONTRASTING THE FDA (CDER) AND ASHP DRUG SHORTAGE WEBSITES: WHAT ARE THE DIFFERENCES? (2014), <http://www.ashp.org/DocLibrary/Policy/DrugShortages/FDA-versus-ASHP.pdf>.

237. 21 U.S.C. § 353b(a)(2)(A)(ii) (2013).

238. Since outsourcing facilities are exempt from manufacturing requirements (e.g., NDA) that are very time consuming (i.e., years), customized drug compounds would be made quicker upon order. See *supra* notes 25, 42.

supplying the needed drugs in shortage will depend on FDA's list of bulk drug substances.

Each year from 2007 to 2011, there was an increase in reported new drug shortages with a record of 255 shortages in 2011.²³⁹ Although 2012 saw the lowest number of reported drug shortages since 2006 (195 shortages), the number of active drug shortages²⁴⁰ was still very high.²⁴¹ The number of active shortages tripled between 2007 and 2012—from 154 in 2007 to 456 in 2012.²⁴² This demonstrates that shortages are lasting longer.²⁴³ The average duration of drug shortages from 2007 to June 2013 was 340 days.²⁴⁴

Of these drug shortages, many were considered critical because no alternatives were available to substitute the products in shortage.²⁴⁵ Most of these shortages involved either generic sterile injectable drugs or drugs from classes associated with more critical health care situations, such as anesthesia, cardiovascular, and anti-infective.²⁴⁶ As a consequence, hospitals and clinics increasingly relied on compounding pharmacies to fill those gaps and provide uninterrupted health care in their facilities.²⁴⁷

After the passage of the DQSA, outsourcing facilities can continue to provide drugs in shortage reliably and safely, but it will depend on FDA's compilation of bulk drug substances.²⁴⁸ Under the DQSA, an outsourcing facility can

239. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-14-194, DRUG SHORTAGES: PUBLIC HEALTH THREAT CONTINUES, DESPITE EFFORTS TO HELP ENSURE PRODUCT AVAILABILITY 11 (2014) [hereinafter GAO DRUG SHORTAGE REPORT].

240. Active drug shortages = newly reported shortages + ongoing shortages that may have started in prior years. *Id.* at 13 n.29.

241. *Id.* at 11, 13.

242. *Id.* at 13–14.

243. *See id.* at 14 (showing in 2007, of the 154 active shortages only 40 were ongoing shortages versus in 2012, of the 456 active shortages, 261 were ongoing shortages).

244. *Id.* at 12.

245. GAO DRUG SHORTAGE REPORT, *supra* note 239, at 14; *see also* Guharoy, *supra* note 29, at 898 (highlighting that in a 2012 survey of 3,063 anesthesiologists, 7% had to postpone and 4% had to cancel because of anesthetic shortage); *see also* Jennifer C. Goldsack, *Impact of Shortages of Injectable Oncology Drugs on Patient Care*, 71 AM. J. HEALTH-SYS. PHARM. 571, 572 (2014) (illustrating the significant rates in delays of chemotherapy due to drug shortages).

246. GAO DRUG SHORTAGE REPORT, *supra* note 239, at 14–16 (nothing that anesthetic and central nervous system, anti-infective, and cardiovascular agents are the top three classes of drugs in shortage at 17%, 16%, and 12% respectively). Examples of central nervous system drugs in shortage include propofol and diazepam; anti-infective drugs in shortage include acyclovir and doxycycline; cardiovascular drugs in shortage include nitroglycerin and verapamil. *Id.* at 16 n.32.

247. *Id.* at 18–19.

248. 21 U.S.C. § 353b(a)(2)(A)(ii) (2013). A bulk substance is “any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.” 21 C.F.R. § 207.3(a)(4) (2015).

compound using a bulk drug substance as long as that bulk substance is on FDA's Section 503B Bulk List.²⁴⁹

For FDA, there must be a significant and substantial reason to allow an outsourcing facility to produce a drug product that may already be available by a manufacturer.²⁵⁰ After two *Federal Register* notices in December 2013 and July 2014, many bulk drug substances were nominated and rejected by FDA.²⁵¹ As of October 2015, FDA published another notice in the *Federal Register* for nominations directing interested parties to give a detailed report of why a specific bulk drug substance should be on the Section 503B Bulk List:

A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat;

A list of FDA-approved drug products, if any, that address the same medical condition;

If there are any FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary;

If the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product;

A bibliography of safety and efficacy data for the drug product compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature; and

If there is an FDA-approved drug product that includes the bulk drug substance nominated, and explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.²⁵²

The alternative to compounding copies of FDA approved products from bulk drug substances is if an ingredient is on the drug shortage list at the time of compounding, distribution, and dispensing of the compounded product.²⁵³ This service may become invaluable to the current state of health care, as the number

249. 21 U.S.C. § 353b(a)(2)(A) (2013).

250. U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: INTERIM POLICY ON COMPOUNDING USING BULK DRUG SUBSTANCES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 3 (Oct. 2015) [hereinafter BULK SUBSTANCES GUIDANCE] (emphasizing that a bulk substance must have a clinical need in order to be nominated).

251. BULK SUBSTANCES GUIDANCE, *supra* note 250, at 3–4 (noting that each notice had over 2,000 nominations and most of them were rejected due to various reasons including not being a bulk drug substance, being a biological drug as opposed to being a small molecule chemical drug, being withdrawn from the market, or not including sufficient information for evaluation).

252. Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket, 80 Fed. Reg. 65770 (Oct. 27, 2015).

253. 21 U.S.C. § 353b(a)(2)(A)(ii) (2013).

of drug shortages remains high.²⁵⁴ However, at the rate FDA is compiling a bulk drug substance list, it seems like it will be some time until outsourcing facilities will be able to freely compound from bulk substances and target drug shortages. Although FDA's interim guidance states that FDA will not take action on an outsourcing facility compounding with a bulk drug substance not on the Section 503B Bulk List and not on the drugs shortage list until the agency finalizes its list and guidance,²⁵⁵ it would be prudent for FDA to issue a bulk substance list that will always be revisable so that outsourcing facilities will not take advantage of this grace period.

V. CONCLUSION

The health crisis created by NECC demonstrated three major issues in drug compounding: the need for regulatory clarity, uniform standards, and a new category of drug distributors. The DQSA attempts to address these problems by clearly establishing FDA authority over a new class of drug distributors called outsourcing facilities.²⁵⁶ An outsourcing facility is neither a pharmacy nor a manufacturer. An outsourcing facility is a unique in-between entity that needs to register with FDA and follow strict CGMP requirements similar to a manufacturer, but it has the flexibility to create drug products without going through the pre-market approval process.²⁵⁷

As of April 2016, there are fifty-nine registered outsourcing facilities.²⁵⁸ Since the enactment of the DQSA, FDA has been busy exercising its restored authority over large-scale compounding. So far, the agency has conducted over 230 inspections of compounding facilities (of which sixty were outsourcing facilities), issued over seventy-five warning letters, and overseen over eighty-five recalls where some resulted in ceasing operations.²⁵⁹ However, more than regulatory enforcement is needed. FDA needs to join forces with state authorities to clarify each other's roles, decide what types of licensure or registration will be necessary beyond federal registration as an outsourcing facility, and identify uniform standards for all aspects of compounding, including repackaging. Moreover, FDA needs to develop a bulk drug substance list for outsourcing facilities in a timely fashion so that outsourcing facilities have the opportunity to help alleviate drug shortages sooner than later. Outsourcing facilities can fulfill the niche

254. See *supra* text accompanying notes 242–243.

255. BULK SUBSTANCES GUIDANCE, *supra* note 250, at 7.

256. See *supra* Part II.B.

257. 21 U.S.C. § 353b(a) (2013); see also CGMP GUIDANCE, *supra* note 127, at 2.

258. *Registered Outsourcing Facilities*, U.S. FOOD & DRUG ADMIN. (last updated Apr. 8, 2016), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>.

259. Jane Axelrod, Associate Director of Policy, CDER and Agency Lead on Compounding, Food & Drug Law Institute Presentation: Title I Implementation—Pharmacy Compounding in 2016 (Feb. 23, 2016).

that contemporary health care needs has created by providing customized drug products quickly and safely for specific subsets of patients. Sterile compounded drugs will help provide uninterrupted health care.

The DQSA is the legal clarity needed to address the issues of large-scale compounding and has the potential to prevent another NECC incident. However, it is up to FDA (in close partnership with the states) to efficiently and effectively enforce the law to pursue the goal of safe production and distribution of sterile compounds nationwide. FDA has an essential role in evolving the new law so that inherent safety will lead to a protected marketplace where compounds will become reliable sources of drug products and alternatives to manufactured drug products. The DQSA is a much-needed step forward for contemporary health care that will use compounding as a form of delivering consistently safe drugs.