

## **A FALSE SENSE OF SAFETY: HOW THE DRUG QUALITY AND SECURITY ACT FAILS TO PROTECT PATIENTS FROM HARM**

### **ABSTRACT**

*For many years, the art of pharmaceutical compounding in the United States has been largely an overlooked and under regulated industry providing millions of patients each year with customized medications. Only after piecemeal enforcement resulted in hundreds of injuries and deaths in an event known as the New England Compounding Center Tragedy, did legislators and regulatory agencies refocus attention on current regulations in pharmaceutical compounding. Congress passed the Drug Quality and Security Act providing clarification for state and federal agencies as to their specific regulatory authority and responsibility to ensure patient safety in pharmaceutical compounding. However, the Drug Quality and Security Act instead created an ineffective and inefficient voluntary registration system, missed opportunities to ensure safer compounded pharmaceutical products, and did not provide other mechanisms or additional resources to aid state agencies in regulation and to increase patient-safety of compounded medications. This comment hopes to elaborate and identify several of the problems legislators at the state and federal level have seemingly overlooked and to suggest regulatory actions that may be taken to improve overall safety of all compounded preparations and the patients that receive them.*

## I. INTRODUCTION

In 2013, over \$329,000,000,000 was spent on prescription drugs in the United States (U.S.).<sup>1</sup> The Centers for Disease Control (CDC) estimates that almost fifty percent of the U.S. population has utilized a prescription drug in the preceding month,<sup>2</sup> and many infants in the U.S. today receive a prescription medication just minutes after birth.<sup>3</sup> Today, pharmacy professionals utilize their advanced training, knowledge of evidence-based medicine, and other technical and computer-based programs to help ensure that pharmaceutical drugs are delivered safely to patients. Therefore, pharmacy professionals are held to high standards by multiple government and private accreditation agencies;<sup>4</sup> however, even with these practical safeguards and agency regulations, there are still areas of pharmacy that are susceptible to endangering public health. After all, it takes just one negligent pharmacy to poison the public's trust. The New England Compounding Center's (NECC) pharmacy operation was one such case.<sup>5</sup>

In one of the worst pharmaceutical tragedies, a single compounding pharmacy was responsible for more than 438 cases of fungal meningitis and thirty-two deaths in the span of fewer than two months, a number that would grow over the next year.<sup>6</sup> In 2012, NECC, located in Framingham, Massachusetts, manufactured and sold thousands of vials of a bacterially contaminated steroid solution to physicians for treatments of patients across the country.<sup>7</sup> This tragedy, however, was preventable. Lax inspections, failure to appropriately follow up on concerns about the inherent and associated risks of drug compounding, and failures in regulatory standards were all contributing factors.<sup>8</sup> For instance, the Federal Food and Drug Administration

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1. IMS INST. FOR HEALTHCARE INFORMATICS, MEDICINE USE AND SHIFTING COSTS OF HEALTHCARE: A REVIEW OF THE USE OF MEDICINES IN THE UNITED STATES IN 2013 30 (2014).

2. See CTRS. FOR DISEASE CONTROL & PREVENTION, HEALTH, UNITED STATES, 2013 21 (2014).

3. See Carol A. Miller et al., *Controversies Concerning Vitamin K and the Newborn*, 112 PEDIATRICS 191, 191 (2003).

4. See generally ACCREDITATION COUNCIL FOR PHARMACY EDUC., ACCREDITATION STANDARDS AND KEY ELEMENTS FOR THE PROFESSIONAL PROGRAM IN PHARMACY LEADING TO THE DOCTOR OF PHARMACY DEGREE iii (2015).

5. See generally Mary A. O'Connor, *The New England Compounding Center*, J. LEGAL NURSE CONSULTING, Spring 2013, 1, 39.

6. *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak: Hearing Before the S. Comm. on Health, Educ., Labor & Pensions*, 112th Cong. (2012) (statement of Margaret A. Hamburg, Commissioner of Food & Drugs, Food & Drug Administration), <http://www.fda.gov/NewsEvents/Testimony/ucm327667.htm> [hereinafter Hamburg Testimony].

7. *Id.*; see also *Multistate Outbreak of Fungal Meningitis and Other Infections*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/hai/outbreaks/meningitis.html> (last updated Feb. 18, 2016).

8. See O'Connor, *supra* note 5, at 39.

(FDA) inspected NECC in 2002,<sup>9</sup> issued a warning letter in 2006,<sup>10</sup> and held these concerns about the pharmacy's actions until the tragedy was discovered.<sup>11</sup> However, the Massachusetts State Board of Pharmacy's (MSBP) 2011 inspection of NECC found their sterile processing areas to be "[s]atisfactory."<sup>12</sup> Despite "inspections" and continued complaints about NECC, action that could have prevented this tragedy was not taken.<sup>13</sup> The NECC tragedy highlights just one of many examples that gives patients alarm and grounds for stricter regulatory processes and more thorough inspections.

Pharmaceutical compounding is the process by "which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient."<sup>14</sup> Furthermore, compounds are divided into two categories within the profession: non-sterile and sterile compounds.<sup>15</sup> Compounds that are considered non-sterile are preparations like oral liquids, tablets, topical creams and gels, suppositories, and troches.<sup>16</sup> Non-sterile compounds require procedures to prevent the risk of outside contaminants; however, they do not need to be performed in a truly sterile (or bacteria/fungal free) environment.<sup>17</sup> On the other hand, sterile compounded products need to be completely free of bacteria and other endotoxins, which if present may cause infection or disease to the patient.<sup>18</sup> Sterile compounds require complex operating procedures, expensive facilities and equipment, and skillful and meticulous manipulations carried out by compounding personnel to ensure safety and efficacy.

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9. H.R. COMM. ON ENERGY & COMMERCE, 113TH CONG., FDA'S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED OPPORTUNITIES? 7 (2013).

10. *Id.* at 10.

11. *Id.* at 39.

12. Hamburg Testimony, *supra* note 6; see also THE COMMONWEALTH OF MASS. DEP'T OF PUB. HEALTH, NEW ENGLAND COMPOUNDING PHARMACY, INC. (NEW ENGLAND COMPOUNDING CENTER) – INSPECTION REPORT, DATED 5/24/11 (2011).

13. See generally H.R. COMM. ON ENERGY & COMMERCE, *supra* note 9.

14. *Compounding and the FDA: Questions and Answers*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm> (last updated Oct. 6, 2015).

15. *Frequently Asked Questions About Pharmaceutical Compounding*, AM. PHARMACISTS ASS'N, <http://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding> (last updated Nov. 19, 2012).

16. BONNIE S. BACHENHEIMER, AM. SOC'Y OF HEALTH-SYSTEM PHARMACISTS, *MANUAL FOR PHARMACY TECHNICIANS* 369-73 (4th ed. 2011). Troches are a type of gelatin dissolving tablet that you place in your mouth and allow to "melt." *Id.* at 372.

17. See <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, USP38-NF33, 2-3, 4 (U.S. Pharmacopeial Convention 2015).

18. See *id.*

According to 2003 estimates by the FDA, only one percent of prescriptions were compounded in the U.S.<sup>19</sup> While that number is most likely outdated due to the surge in bio-identical hormone replacement, manufacturer shortages, and other consumer pushes for compounded medication, even one percent of retail only prescriptions in 2014 would be equivalent to around forty million prescriptions.<sup>20</sup> This number also does not include prescriptions compounded in a hospital, a doctor's office, or those compounded in a retail setting and sold to the hospital, which could ultimately double the final tally.<sup>21</sup> More recently, the National Community Pharmacists Association (NCPA)<sup>22</sup> conducted a national survey of independent community pharmacies in November 2012.<sup>23</sup> Results showed that seventy-two percent of those pharmacies engaged in compounding provided non-sterile compounding services only; thirty-eight percent of the pharmacies compounded five percent or more of their total prescription count.<sup>24</sup> Extrapolating this to the more than 23,000 pharmacies NCPA represents,<sup>25</sup> it is clear that compounding is prevalent in the practice of pharmacy.

Compounding pharmacy has been historically overlooked by federal agencies and gained differing levels of enforcement from state boards of pharmacy (SBOP). However, in response to the 2012 NECC tragedy, Congress

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19. *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. (2003) (statement of Steven K. Galson, Acting Director, Center for Drug Evaluation & Research, Food & Drug Administration); *What is Compounding?*, INT'L ACAD. COMPOUNDING PHARMACISTS, <http://www.iacprx.org/default.asp?page=1> (last visited Mar. 3, 2016).

20. It is estimated that four billion retail prescriptions were filled in 2014. *State Health Facts: Total Number of Retail Prescription Drugs Filled at Pharmacies*, KAISER FAM. FOUND., <http://kff.org/other/state-indicator/total-retail-rx-drugs/> (last visited Jan. 8, 2016).

21. *Id.*

Data shown here are for calendar year 2014 and include the number of prescription drugs filled at retail pharmacies only. Data are based on IMS's Vector One® database which collects data from a panel of retail pharmacies, third party payers, and data providers. Retail pharmacies include independent pharmacies, chain pharmacies, food stores, and mass merchandisers found in 814 defined regional zones. These totals include prescriptions filled at pharmacies only and a small portion of over-the-counter medications and repackagers and exclude those filled by mail order.

*Id.*

22. "NCPA represents the interests of pharmacist owners, managers, and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs." NAT'L CMTY. PHARMACISTS ASS'N, *Community Pharmacy Compounding Survey November 2012* (2012), <http://www.ncpanet.org/pdf/Survey-compounding-results.pdf>.

23. *Id.*

24. *Id.*

25. *Id.*

focused attention on compounding and passed the Drug Quality and Security Act (DQSA) a year later.<sup>26</sup> The Act implements important changes to the nature of pharmacy regulation, but it is incomplete. Its reactive response misses real opportunities that could ensure a NECC-type tragedy will not happen again and leaves uncertainty in nationwide enforcement of compounding pharmacy.

The goal of this comment is to analyze and address the holes in the regulation of compounding pharmacy that ensure product quality and patient safety, and to identify Congress's missed opportunities in the passage of the DQSA. Section I of this comment is an introduction into pharmaceutical compounding. Section II of this comment begins by briefly describing the origins of pharmaceutical compounding, followed by Section III, which describes some of the most likely ways compounds may be incorrectly prepared and result in harm to patients. Section IV then discusses regulatory authority and past enforcement of compounding on the federal and state levels. Section V then analyzes a part of the DQSA that is intended to regulate compounding and the registration process it creates for sterile compounders. Section VI points out regulatory failures and the issues not addressed, or missed in legislating the DQSA. The comment will then conclude with Section VII, discussing possible remedies and actions that state and federal agencies may take to increase compounding quality and safety.

## II. A BRIEF HISTORY OF COMPOUNDING

The art of compounding originated in ancient Egyptian and Roman times when healers mixed herbs, roots, and other ingredients to make remedies intended to cure illnesses faced by their community.<sup>27</sup> Some remedies were naturally successful, while others caused harm to the patient.<sup>28</sup> As understanding of these remedies progressed, the process was formalized into the profession of pharmacy.<sup>29</sup> The profession started like many others, where pharmacists trained as apprentices, but then a curriculum of pharmacy was later formalized into a higher education setting.<sup>30</sup> In 1820, the newly founded

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26. See Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013) [hereinafter Drug Quality and Security Act].

27. See generally Edward Kremers, KREMERS AND URDANG'S HISTORY OF PHARMACY 3 (Glenn Sonnedecker ed., 4th ed. 1976); see also DAVID L. COWEN & WILLIAM H. HELFAND, PHARMACY: AN ILLUSTRATED HISTORY 23 (Harry N. Abrams ed., 1990).

28. See generally COWEN & HELFAND, *supra* note 27.

29. See generally *id.*

30. Joseph L. Fink, *Pharmacy: A Brief History of the Profession*, STUDENT DR. NETWORK (Jan. 11, 2012), <http://www.studentdoctor.net/2012/01/pharmacy-a-brief-history-of-the-profession/>. The first school of pharmacy was founded in Philadelphia in 1821. *Id.* Originally, students could obtain a Graduate in Pharmacy (Ph.G.) degree with only fifty-two total weeks of study or a Pharmaceutical Chemist (Ph.C.) degree after seventy-two weeks. *Id.* Eventually the standard

U.S. Pharmacopeia Convention established a book known as the United States Pharmacopeia (USP), which served as a reference for information about chemicals “most fully established and best understood.”<sup>31</sup> Pharmacists used the USP as one of several aids to prepare and manipulate medications from raw drug chemicals into prescription drugs.<sup>32</sup> This preparation, commonly known as compounding, accounted for most medication before the 1950’s, including prescriptions written by doctors and those created independently when patients secured remedies straight from the pharmacist.<sup>33</sup> Beginning in the late 1950’s and early 1960’s, the large scale manufacturers began to push the role of pharmacists away from compounding to dispensing commercially manufactured drugs as more patients were starting treatments for chronic and quickly diagnosable acute diseases.<sup>34</sup> By 1990, nearly all over-the-counter drugs and prescription medications were commercially manufactured rather than compounded in the corner drugstores leading to enhanced regulatory power of the FDA to ensure uniformity and quality of medications.<sup>35</sup> The move to manufactured medications also allowed the industry to provide mass treatments of many medical conditions, and spurred research and development of other drugs not at the time listed in the USP.

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became a four-year Bachelor of Science in Pharmacy (B.S.Pharm.), and as of the 1990’s, the only degree qualifying a student to become licensed as a pharmacist is the Doctorate of Pharmacy degree (Pharm.D). *Id.*

31. *USP Our History*, U.S. PHARMACOPEIAL CONVENTION, <http://www.usp.org/about-usp/our-history/usp-milestones-timeline> (last visited Feb. 10, 2015). The USP may also be referred to by others as the USP-NF or the USPDI. In 1975, the USP purchased the National Formulary from the American Pharmacists Association and changed the name to USP-NF. *Id.* Before 1975, the National Formulary (NF) was a separate guidebook that contained information on the properties of herbs, roots, and other chemicals that had medicinal properties. *Id.* For purposes of this article the term USP and USP-NF will be used interchangeably as practitioners commonly do. *Id.*

32. See GEETA TIRUMALAI & ANGELA LONG, UNITED STATES PHARMACOPEIAL CONVENTION: RESPECTING THE PAST, MOVING CONFIDENTLY INTO THE FUTURE (2013), [http://www.usp.org/sites/default/files/usp\\_pdf/EN/aboutUSP/usp\\_history\\_final\\_with\\_acknowledgement.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/aboutUSP/usp_history_final_with_acknowledgement.pdf).

33. Peter Younkin, *Making the Market: How the American Pharmaceutical Industry Transformed Itself in the 1940s* 1, 5 (Nov. 2008) (unpublished manuscript), <http://faculty.chicago-booth.edu/workshops/orgs-markets/past/more/pdf/YounkinJan09.pdf>. See generally Durham-Humphrey Amendment, Pub. L. No. 215, 65 Stat. 648 (amending §§ 303 (c) and 503(b) of the Federal Food, Drug, and Cosmetic Act, codified in scattered sections of Title 21 U.S.C.); Virgil Van Dusen & Alan R. Spies, *A Review of Federal Legislation Affecting Pharmacy Practice*, PHARMACY TIMES (Dec. 1, 2006), <http://www.pharmacytimes.com/publications/issue/2006/2006-12/2006-12-6154>.

34. See Jesse M. Boodoo, *Compounding Problems and Compounding Confusion: Federal Regulation of Compounded Drug Products and the FDAMA Circuit Split*, 36 AM. J. L. & MED. 220, 222 (2010).

35. *Id.* at 221-22.

However, the art of compounding medications was never completely lost by the pharmacy profession. In 1981, Professional Compounding Centers of America (PCCA) was created with the goal of reviving the practice of compounding to the profession.<sup>36</sup> Doctor and patient demands for medications free of potential allergens (due to additives), medications requiring specific dosage forms (large pills to liquids), and specialized dosages of medications not commercially available, all contributed to the re-growth of compounding in the practice of pharmacy.<sup>37</sup>

With the revitalization of compounding there came a new categorization of compounding pharmacy. Compounders in the business were now viewed as falling into one of two categories: traditional compounders or non-traditional (or pirate manufacturing) compounders.<sup>38</sup> Traditional compounders were those pharmacists who prepared just enough of a patient specific compound or sometimes made a little extra in anticipation of prescribing patterns from local doctors.<sup>39</sup> Compounders that stretched this “anticipatory need” and made excessive quantities of medications were categorized as non-traditional, or “pirate-manufacturers.”<sup>40</sup> These non-traditional compounding pharmacies grew more numerous and eventually large quantities of compounded drugs were regularly shipped to patients across the U.S. instead of being dispensed to their local communities. Coupled with a spur in the understanding of hormone replacement therapy (HRT) in the 1990’s and early 2000’s, further demands for compounding produced lucrative business ventures for pharmacists because not many HRT drugs were commercially available in specific dosages.<sup>41</sup> This niche attracted new attention to the practice of compounding and created questions regarding large-scaled compounding safety and legality.

### III. THE RISKS AND CURRENT SAFETY MEASURES IN COMPOUNDING MEDICATIONS

There are inherent risks associated with unregulated and poor quality compounding. Compounding is both art and science and may pose serious patient safety risks if not executed properly. The risks that compounders most commonly encounter are those surrounding potency, contamination,

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36. Prof'l Compounding Ctrs. of Am., *What is PCCA?*, <http://www.pccarx.com/patients/what-is-pcca-patients> (last visited Jan. 31, 2016).

37. See Tamira Mullarkey, *Pharmacy Compounding of High-Risk Level Products and Patient Safety*, 66 AM. J. HEALTH-SYS. PHARM. S4, S4-S5 (2009).

38. See Boodoo, *supra* note 34, at 229-30.

39. See *id.* at 223-34.

40. *Id.* at 229.

41. Bruce Patsner, *Pharmacy Compounding of Bioidentical Hormone Replacement Therapy (BHRT): A Proposed New Approach to Justify FDA Regulation of These Prescription Drugs*, 63 FOOD & DRUG L.J. 459, 459 (2008).

overmedication, and medication-replacement.<sup>42</sup> These risks are also intensified when compounders produce mass quantities—as larger batches usually equal larger errors.<sup>43</sup> “Unlike [commercial] drug manufacturers who are required to demonstrate the safety, efficacy, strength, quality, and purity of their proposed products via the FDA’s New Drug Application, drug compounders design and distribute their products easily and unrestrictedly . . . without pre- or post-market testing.”<sup>44</sup> The FDA acknowledges that the average pharmacist compounding a drug product does not have to adhere to Current Good Manufacturing Practices (CGMP)<sup>45</sup> that drug manufacturers must adhere to,<sup>46</sup> however, compounders must adhere to the safeguards set forth in the USP’s general chapters.<sup>47</sup> CGMPs help to curtail the five most common risks to patients when preparing large-scale drug products, but similarly, traditional

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42. *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. (2003) (statement of Sarah Sellers, Executive Director, The Center for Pharmaceutical Safety); Boodoo, *supra* note 34, at 225.

43. *Id.* at 230.

44. *Id.* at 225.

45. *Id.*

CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

*Facts About the Current Good Manufacturing Practices (CGMPs)*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm> (last visited Feb. 17, 2015).

46. *See generally* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CURRENT GOOD MANUFACTURING PRACTICE – INTERIM GUIDANCE FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT (2014); *Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm> (last updated Dec. 17, 2014).

47. USP General chapters below <1000> are considered requirements, while those chapters above <1000> are considered suggested practices. USP <795> (covering non-sterile compounding) and USP <797> (covering sterile compounding) are the standards in which traditional compounding pharmacists are to use when preparing compounding medications. These practices include ensuring the proper storage of chemicals, using proper production devices, implementing quality controls on sterility and potency, etc. U.S. PHARMACOPEIAL CONVENTION, U.S. PHARMACOPEIA – NATIONAL FORMULARY 3 (34th ed. 2011).

compounders (likely lower-volume producers) can avoid these risks with strict adherence to the USP guidelines.

#### A. Potency

A compounded drug product is said to have an acceptable potency when a test indicates that there is ninety to 110% of the labeled strength of every active pharmaceutical ingredient (API) in the preparation.<sup>48</sup> Therefore an acceptably “potent” commercially manufactured or compounded drug may contain fluctuations in API content, however, potency outside this range labels the drug to be either sub- or superpotent.<sup>49</sup>

The FDA is aware of potency issues and has conducted several studies of compounded drug products over the years, including a survey in 2001 and another in 2006.<sup>50</sup> Both FDA surveys noted that about one-third of compounded medications were outside of the accepted potency ranges federally recognized by the USP.<sup>51</sup> A majority of those compounds tested included drugs containing hormones, drugs for inhalation, and local anesthetic products—the outliers ranged in potency from less than seventy percent to more than 260% of their labeled value.<sup>52</sup> These tests demonstrate a need for concern as taking any medication that is two to three times more potent than prescribed and labeled can pose serious problems and unwanted side effects.<sup>53</sup> Compounders that use drugs with narrow therapeutic indices<sup>54</sup> could therefore cause potentially deadly consequences when double or triple dosed. For instance, patients could experience arrhythmias and seizures if taking a

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48. Press Release, Updated FDA Statement on Compounded Versions of Hydroxyprogesterone Caproate (the active ingredient in Makena) (June 15, 2012).

49. *See id.*

50. Galson, *supra* note 19; *2006 Limited Survey of Compounded Drug Products*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm> (last updated Mar. 22, 2010) [hereinafter *2006 Limited Survey*].

51. *See 2006 Limited Survey, supra* note 50; *USP-NF*, U.S. PHARMACOPEIAL CONVENTION (2016), <http://www.usp.org/usp-nf> (“The U.S. Federal Food, Drug, and Cosmetics Act designates the USP-NF as official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP–NF to avoid possible charges of adulteration and misbranding.”).

52. *2006 Limited Survey, supra* note 50. These products tested included both sterile and non-sterile compounds. *Id.*

53. *See generally id.*

54. A drug with a narrow therapeutic index is a drug in which:

there is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or have less than a 2-fold difference in the minimum toxic concentrations and the minimum effective concentrations in the blood and safe and effective use of the drug products requires careful dosage titration and patient monitoring.

21 C.F.R. § 320.33(c) (2015).

compounded theophylline capsule that is actually three times the labeled potency.<sup>55</sup> However, pharmacists have many ways to overcome drug potency problems. Utilizing only chemicals stored properly and within the expiration date, ensuring precise measurements of all ingredients, developing and implementing quality control standards,<sup>56</sup> and utilizing outside laboratories<sup>57</sup> to test product potency, are all highly recommended in the practice and encouraged by the USP standards.<sup>58</sup>

However, despite the known problems associated with potency in compounded medications, potency testing is not required for all compounded products under USP or FDA guidelines for compounders as it could unduly burden the pharmacy.<sup>59</sup> Moreover, because of the cost,<sup>60</sup> some pharmacies may skip this step and seldom check any potencies, while other pharmacies are required to test as part of their independent accreditations.<sup>61</sup> For example, the Pharmaceutical Compounding Accreditation Board (PCAB) requires, among many other compounding safeguards, accredited pharmacies to show evidence that one preparation per dosage form was tested for potency every six months as a quality control measure.<sup>62</sup> While it may seem like a minimal standard, consistent potency testing of randomized products allows traditional pharmacies to identify potential problems in procedure and maximize processes to ensure patient safety. Regardless of the price, compounders

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55. *Theophyllines*, DRUGS.COM (2016), <http://www.drugs.com/monograph/theophyllines.html>.

56. *See* <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 17, at 5, 8. Standardized compounding practices and formulas are essential guidelines for technicians and pharmacists who engage in compounding. *Id.* at 1. These help to provide standardization at each pharmacy. *Id.*

57. Loyd V. Allen, *Potency and Stability Testing*, SCI. & TECH. (2013), [https://compoundingtoday.com/Newsletter/Science\\_and\\_Tech\\_1303.cfm](https://compoundingtoday.com/Newsletter/Science_and_Tech_1303.cfm). Potency testing can be performed through a number of outside laboratories. *See, e.g.*, Bill J. Zolner, *Stating a Testing Program*, EAGLE ANALYTICAL SERVS., <http://www.eagleanalytical.com/sitecontent/590/featured-video.aspx> (last visited Feb. 10, 2015) (recommending that you test five percent monthly of compounds for quality control).

58. *See* <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 17, at 7.

59. *See generally id.*; <797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, USP38-NF33 (U.S. Pharmacopeial Convention 2015) (stating that sterile compounds need to be tested according to <71> *Sterility Tests*).

60. Potency tests generally start around \$160 and can run upwards from there depending on the amount of ingredients in the preparation. *See, e.g.*, Invoice from Dynalabs to Tri-State Compounding Pharmacy, LLC (Dec. 17, 2015) (on file with author).

61. PHARMACY COMPOUNDING ACCREDITATION BD., PCAB ACCREDITATION MANUAL 33 (2011) [hereinafter PCAB ACCREDITATION MANUAL].

62. *Id.* at 17, 47 (dosage forms may include capsules, troches, gels, creams, ointments, solutions, etc.).

should consider that mistakes resulting in patients being over- or under-dosed can harm patients and lead to compounding liability.<sup>63</sup>

### B. Contamination

As the NECC meningitis outbreak demonstrated, contamination is another potentially harmful and deadly risk associated with compounding although it is mostly an issue for sterile products.<sup>64</sup> In 2012, the FDA was notified of a “cluster of meningitis cases at a single clinic” by the Tennessee Department of Health.<sup>65</sup> The FDA’s investigation of NECC showed fungal contamination in the steroid injections from NECC and issued a MedWatch Safety Alert to over 220,000 health professionals on October 5, 2012.<sup>66</sup> At the time of Margaret Hamburg’s testimony before the U.S. Senate on November 15, 2012, the CDC had reported thirty-two deaths in 438 cases of meningitis and peripheral joint infections across nineteen states.<sup>67</sup> That number continued to grow in the months to follow reaching 751 reported cases and sixty-four deaths.<sup>68</sup> Furthermore, the Massachusetts Department of Public Health and FDA joint investigation and inspection noted a slew of USP violations.<sup>69</sup>

USP guidelines for sterile preparations allow compounders to greatly reduce the risk of contamination, yet sometimes these guidelines are overlooked for cost and technical challenges of implementation.<sup>70</sup> However, the USP requires that sterile compounded products are tested for contamination and provides certain benchmarks for compounders.<sup>71</sup> Unfortunately, because sterile drug compounds can be highly lucrative, it is not unusual for pharmacies to make a batch of sterile compounds, or in NECC’s case—

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63. Boodoo, *supra* note 34, at 225-26 (stating that a patient was admitted to the hospital for twenty-five days when he ingested a compounded capsule containing over 1000% of the labeled API in it).

64. Hamburg Testimony, *supra* note 6.

65. *Id.*

66. *Id.*

67. *Id.*

68. Press Release, Dep’t of Justice, 14 Indicted in Connection with New England Compounding Center and Nationwide Fungal Meningitis Outbreak (2014), <http://www.justice.gov/opa/pr/14-indicted-connection-new-england-compounding-center-and-nationwide-fungal-meningitis>.

69. See MASS. DEP’T OF PUB. HEALTH, NEW ENGLAND COMPOUNDING CENTER (NECC) PRELIMINARY INVESTIGATION FINDINGS 4 (2012).

70. See generally <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 17.

71. See generally <71> STERILITY TESTS, U.S. PHARMACOPEIAL CONVENTION, USP38-NF33, 125 (U.S. Pharmacopeial Convention 2015). See also <797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS, *supra* note 59.

hundreds of batches, without the proper equipment, procedures, or testing of finished drug products.<sup>72</sup>

### C. *Overmedication and Medication Replacement*

Overmedication may occur when a physician prescribes an excessive amount of a medication or prescribes an altogether unnecessary medication.<sup>73</sup> Most of the time, prescriptions resulting in overmedication or inappropriate medication replacement are due to patient requests,<sup>74</sup> and the physician or pharmacist is either unaware of other medications the patient is taking, or what interactions occur between commercially manufactured and compounded medications.<sup>75</sup> Overmedication can also occur when a patient uses too much of a medication, intentionally or unintentionally, or if a pharmacist incorrectly counsels or fills the medication.<sup>76</sup> Prescription verification and reconciliation procedures allow a pharmacist to recognize the danger to the patient; however, the pharmacist must be trained in advanced compounding practices to understand just how much of the drug the patient is absorbing via a specific cream, capsule, etc. Medication-replacement has also become one way patients are trying to obtain natural (preservative free or non-commercial) remedies as a substitute for manufactured products and thus leading to a growth in compounding.<sup>77</sup> Sometimes these “natural” remedies are untested, composed of drugs with no monograph, and have completely bypassed any FDA safety process.<sup>78</sup>

Stewardship of the technical skills and education of advanced compounding practices allows compounders to overcome these challenges. A compounder’s commitment to ongoing evaluation of pharmacy processes and safeguards is therefore critical to keeping patients safe even with great financial incentives to compound and build business fast. However, not all compounders follow these practices—partially because pharmacies slip under the regulatory radar of state boards or federal agencies. Moreover, some

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72. Endotoxin and sterility tests combined run about \$160 per tested substance. Invoice, Dyna-Labs, Inc., Dyna-labs Pricing Guide (2014) (on file with author). Depending on the risk level of the compounded sterile product, USP <797> generally requires sterility and endotoxin testing for certain high-risk compounded sterile products in multi-use vials, batches greater than twenty-five single-dose packages, or those exposed to periods of non-refrigeration. See <797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 59, at 575.

73. Boodoo, *supra* note 34, at 228.

74. John McKinlay et al., *Effects of Patient Medication Requests on Physician Prescribing Behavior: Results of a Factorial Experiment*, 52 MED. CARE 4, 294, 298 (2014).

75. Boodoo, *supra* note 34, at 228.

76. *Id.* at 225.

77. *See id.* at 228.

78. *Id.* at 228-29.

pharmacies have grown too fast, out-pacing safety and quality standards, or have been too greedy, skimping on expensive quality controls. While demand for compounded drug products continues to rise, compounders must ensure they take the proper safeguards in this “lax” regulatory environment or patient harm and compounding failures will continue to increase.

#### IV. FEDERAL REGULATION AFFECTING PHARMACY PRIOR TO THE DQSA

##### A. *Federal Regulation of Medications for Patient Use*

The origins of FDA oversight in pharmaceutical products grew from the Pure Food and Drug Act of 1906 (PFDA).<sup>79</sup> The bill created federal executive authority in an agency to prevent adulterated and misbranded food, drugs, and medication from being manufactured and sold within the U.S.<sup>80</sup> However, in 1937, it became clear that the PFDA was not enough when a company manufacturing sulfanilamide elixir killed over 100 people across the U.S.<sup>81</sup> Congress re-evaluated the PFDA and subsequently passed the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938.<sup>82</sup> The FDCA then introduced more FDA oversight and regulation of new drug products being made and sold in the U.S.<sup>83</sup>

The FDCA required manufacturers of “new drugs” to obtain premarket approval from the FDA for products intended for the mass market.<sup>84</sup> To define what “new” was, the Act adopted the list of drugs in the current USP, however, it made no mention on whether combining two old drugs constituted a new drug.<sup>85</sup> As such, manufacturers and compounders continued producing combinations of USP listed products without going through the “new drug”

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79. John Swann, *FDA's Origin*, FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm> (last updated June 24, 2014).

80. Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906) (deriving federal authority from the Commerce Clause).

81. *See generally* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG., June 1981, <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm>. Sulfanilamide was used to treat streptococcal infections and was marketed in powder and tablet form, however, due to demand for a liquid dosage form, the company experimented and ultimately used diethylene glycol, a component of antifreeze, an unknowingly toxic agent, to dissolve the powder and labeled it an elixir (alcoholic compound). *Id.* Although a pharmacist formulated the product, it was not tested, and it led to a public health disaster. *Id.*

82. *Id.*

83. *Id.*

84. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(a) (2012); *see also* Michael Snow, *Seeing Through the Murky Vial: Does the FDA Have the Authority to Stop Compounding Pharmacies from Pirate Manufacturing?*, 66 VAND. L. REV. 1609, 1615 (2013).

85. *See generally*, 21 U.S.C. §§ 351-360ccc-2 (2012).

pre-market approval process.<sup>86</sup> Under the Act, the FDA had broad authority over all types of drug production, even traditional pharmacies, although it was Congress's primary intent, and the FDA's understanding, that FDCA was aimed to prevent large-scale manufacturers of medications, such as the company producing sulfanilamide, from marketing drugs without approval.<sup>87</sup> However, the FDCA did not expressly carve out the traditional pharmacy practice of compounding, something that would prove troublesome to future compounders in understanding the FDA's actual authority over traditional pharmacies.<sup>88</sup>

For years, the regulation of pharmaceuticals went largely untouched and unchallenged, until Congress again passed the Kefauver-Harris Amendments in 1962 (1962 Amendments).<sup>89</sup> The 1962 Amendments modified the FDCA to require substantial evidence that drugs were safe and effective before being placed into the market.<sup>90</sup> Equally as important to compounders was the 1962 Amendments notation that the "traditional practice" of compounding in pharmacies was exempted, and, therefore, traditional compounders did not need to prove safety and efficacy in compounding to be in compliance with the FDCA.<sup>91</sup> While the "traditional practice" of compounding was most likely understood as applying to individualized patient prescriptions, its vagueness again left regulatory holes that allowed for rapid, but unchecked growth by the compounding industry.

### 1. Compounds as New Drugs

After the 1962 Amendments, the FDA continued its focus on manufacturing and remained largely inactive in its regulation of compounding.<sup>92</sup> However, a further clarification of what was considered a "new drug" under the FDCA brought forth new views of regulation on compounders.<sup>93</sup>

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86. See Snow, *supra* note 84, at 1612.

87. See generally *id.* at 1615.

88. *Id.*

89. Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962) [hereinafter 1962 Amendments]; see also Suzanne Junod, *FDA and Clinical Drug Trials: A Short History*, FOOD & DRUG ADMIN. (2014), <http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm>.

90. See DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUGS AND BIOLOGICAL PRODUCTS 1 (1998), [http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml\\_no\\_dtd&ie=UTF-8&access=p&oe=UTF-8](http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8). See generally 1962 Amendments, *supra* note 89.

91. See generally 1962 Amendments, *supra* note 89, at Part A.

92. Junod, *supra* note 89.

93. See *id.*

Drugs are defined by the FDCA as any “articles recognized in the official United States Pharmacopeia . . . [that are] intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; and . . . intended to affect the structure or function of the body . . .”<sup>94</sup> With these words, Congress adopted the USP as the FDA’s official yardstick in which to measure any chemical drug products.<sup>95</sup> Thus, any new or designed chemicals used to treat a patient’s condition, or to use past chemicals in ways previously not listed under its USP monograph, would trigger a designation of a “new drug” and require review.<sup>96</sup> But still, the definition of “new drug” did not address whether combining two chemicals already listed in the USP qualified.

In 1974, the FDA promulgated 21 C.F.R. § 310.3(h)(1)-(2) and clarified that a drug is “new” even if it is a “combination of two or more substances, none of which is a new drug.”<sup>97</sup> The FDA further stated, that a changed or additional substance used in formulating a compound did not necessarily have to be an active pharmaceutical ingredient,<sup>98</sup> but could be an “excipient, carrier, coating, or other component.”<sup>99</sup> This formalization signaled that unless the compounded combination was exactly as listed in the USP (through FDA approval), down even to inactive ingredients, then the compounded product was considered a “new drug.”

Shortly after, compounding regained its prevalence in the later parts of the 1980’s and 1990’s, some pharmacies started compounding “new drugs” on a large scale, outside the traditional patient specific prescription role.<sup>100</sup> The FDA investigated these pharmacies to find the process of compounding “exact

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94. Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 675, 52 Stat. 1040 (1938) (codified at 21 U.S.C. §§ 301-399d (2012)) *reprinted in* LEGISLATIVE HISTORY OF THE FEDERAL FOOD DRUG & ACT AND ITS AMENDMENTS 453, 453 (1979).

95. 21 U.S.C. §§ 351-360ccc-2 (2012) *supra* note 85 (the FDCA grandfathered drug substances already in the USP); *USP-NF*, *supra* note 51; *see also USP Milestones—A Timeline*, U.S. PHARMACOPEIAL CONVENTION, <http://www.usp.org/about-usp/our-history/usp-milestones-timeline> (last visited Mar. 1, 2016) (stating the USP acquired the NF in 1975). USP-NF publishes a list of drug substances that include monographs, dosage forms, and compounded preparations. *Id.* This list is updated as the FDA accepts new formulations and research. *Id.* *See generally* LOYD V. ALLEN, *THE ART, SCIENCE, AND TECHNOLOGY OF PHARMACEUTICAL COMPOUNDING* 1-19 (Sandra J. Cannon & Nancy Tarleton Landis eds., 4th ed. 2012).

96. *See* *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 395 (5th Cir. 2008).

97. 21 C.F.R. § 310.3(h)(1)-(2) (1974).

98. *Id.* Active pharmaceutical substances are those types of drugs/chemicals that produce a biological response in an individual for therapeutic purposes set forth. S. Kopp, *Definition of Active Pharmaceutical Ingredient* 3-4 (World Health Organization, Working Document QAS/11.426/Rev.1, 2011).

99. 21 C.F.R. § 310.3(h)(1) (1974).

100. *Boodoo*, *supra* note 34, at 232-33.

copies” of already FDA-approved drugs.<sup>101</sup> In response to the large-scale compounders, the FDA issued a Compliance Policy Guide (CPG) in 1992 that reaffirmed their ability to exercise discretionary authority and enforcement practices over compounding pharmacies.<sup>102</sup> To aid compounders in navigating FDA enforcement, the 1992 CPG also provided a list of compounding related activities the FDA would use to assess whether or not a pharmacy was acting like a manufacturer.<sup>103</sup> Activities included:

1. Soliciting business . . . to compound specific drug products, product classes, or therapeutic classes of drug products [;]
2. Compounding, regularly, or inordinate amounts, drug products that are commercially available in the marketplace and that are essentially generic copies of commercially available, FDA-approved drug products[;]
3. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA approved facility[;]
4. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements[;]
5. Using commercial scale manufacturing or testing equipment for compounding drug products[;]
6. Compounding inordinate amounts of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions[;]
7. Offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale[;]
8. Distributing inordinate amounts of compounded products out of state[;]
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.<sup>104</sup>

The FDA also listed possible agency enforcement actions that ranged from issuance of warning letters to criminal charges.<sup>105</sup> The 1992 CPG received pushback from several pharmacy associations seeking to eliminate federal oversight on compounding pharmacies; however, resistance did little but cast uncertainty on the FDA’s ability to use the 1992 CPG as a tool to aid them in their historically limited enforcement of compounding.<sup>106</sup>

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101. *See id.* at 232.

102. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDE FOR FDA STAFF AND INDUSTRY 4 (1992) [hereinafter 1992 CPG]. “[W]hen the scope and nature of a pharmacy’s activity raises the kinds of concerns normally associated with a manufacturer and results in significant violations of the new drug, adulteration, or misbranding provisions of the [FDCA], FDA has determined that it should seriously consider enforcement action.” *Id.*

103. *See id.* at 4-5.

104. *Id.* at 5; Snow, *supra* note 84, at 1616-17; Boodoo, *supra* note 34, at 233.

105. 1992 CPG, *supra* note 102, at 6.

106. Snow, *supra* note 84, at 1616-18.

## 2. Food and Drug Administration Modernization Act

In 1997, Congress again modified parts of the 1938 FDCA by passing the Food and Drug Administration Modernization Act (FDAMA).<sup>107</sup> Most notably, the FDAMA added Section 503A to the FDCA and created a specific section related to pharmacy compounding.<sup>108</sup> The FDAMA stated a limited number of FDCA provisions<sup>109</sup> would not apply to compounding pharmacies that met the requirements of Section 503A.<sup>110</sup> Therefore, the FDAMA created a formal exemption for compounders to the “new drug” review process.<sup>111</sup>

The exemption requirements under FDAMA were merely a formal adaptation of the 1992 CPG and provided three concepts for compounders to follow.<sup>112</sup> The FDAMA specifically exempted compounds from FDA oversight if the compounds that were produced were: (1) patient specific and pursuant to a prescription; (2) limited to anticipatory compounding based on an established pharmacist-physician relationship; (3) and if the pharmacy [did] not distribute more than five percent of [its] total prescription orders . . . out of state.<sup>113</sup>

However, the FDAMA was not the FDA’s silver bullet of clarity for compounding and was almost immediately challenged by pharmacies claiming the marketing prohibition infringed on compounders rights under the First Amendment.<sup>114</sup> On this challenge, the Ninth Circuit invalidated 503A in its entirety in the precursor case to *Western States Medical Center v. Shalala*.<sup>115</sup> The Supreme Court granted certiorari in *Thompson v. Western States Medical Center* and upheld the unconstitutional nature of the marketing prohibition, but did not rule on the severability of the section from 503A in its entirety<sup>116</sup> causing a circuit split.<sup>117</sup> Therefore, 503A was invalid in the Ninth Circuit,<sup>118</sup> but other circuits continued to uphold 503A as valid—striking only the

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107. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 127, 111 Stat. 2296, 2328 (1997) (codified at 21 U.S.C. § 353a (2012)) [hereinafter FDAMA]; Snow, *supra* note 84, at 1618.

108. FDAMA, *supra* note 107, at § 503A; Snow, *supra* note 84, at 1619.

109. FDAMA, *supra* note 107, at § 503A (referencing Sections 501(a)(2)(B), 502(f)(1), and 505 of the FDCA).

110. *Id.*

111. *See id.*

112. *See* FDAMA, *supra* note 107, at § 503A; *see also* Galson, *supra* note 19.

113. *See* FDAMA, *supra* note 107, at § 503A; Snow, *supra* note 84, at 1619.

114. *W. States Med. Ctr. v. Shalala*, 238 F.3d 1090, 1093 (9th Cir. 2000).

115. *Id.* at 1097-98. The court found the marketing prohibition was not severable and therefore the entire act was invalid. *Id.* at 1098.

116. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360 (2002).

117. *Compare Shalala*, 238 F.3d at 1098, *with* *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 409 (5th Cir. 2008).

118. *Shalala*, 238 F.3d at 1098.

provision related to marketing activities.<sup>119</sup> Aside from the challenges and split, the FDA could still have reverted to the definition of “new drugs” in compounding enforcement actions to maintain their authority.<sup>120</sup>

Upon the conclusion of *Thompson* in 2002, the FDA issued yet another CPG regarding compounding practices that suggested a continued enforcement reliance on the factors enumerated in Section 503A, as previously passed through the FDAMA, just without enforcement of the marketing prohibition.<sup>121</sup> The 2002 CPG therefore narrowed the FDA’s focus to specifically those “[p]harmacies engaged in activities analogous to manufacturing and distributing drugs . . . ,” and imposed reliance on the states to take care of “less significant violations of [503A].”<sup>122</sup> Yet again, the CPG gave compounders another non-exhaustive list of nine factors that would be considered before the FDA would elect to take action.<sup>123</sup> Some of these nine factors addressed concerns such as: the quantities of compounds made prior to receiving prescriptions or in commercial scales, whether compounds included drugs removed from market, using substances not confirmed from an FDA registered facility or meeting compendia requirements, making copies of drugs commercial available, and failing to conform with state law regarding the practice of pharmacy.<sup>124</sup>

However, all of these clarifications and rules only muddled the thinking as to how, or if, the FDA would enforce compounding standards in the future even though the FDCA gave the FDA authority to do so. Part of the problem was to be addressed by the FDA’s reliance on the states, however, “pirate-manufacturers” still eluded some state officials and again showed that it was necessary for the FDA to act in some occasions.

### B. State Regulation

Every state has a “pharmacy practice act” that creates authority for a SBOP to oversee the practice of pharmacy within their state.<sup>125</sup> SBOPs generally consist of around ten members—often pharmacists from various backgrounds plus or minus an at large public member, all of whom act as directors for the

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119. Boodoo, *supra* note 34, at 239; *see also* Mukasey, 536 F.3d at 409.

120. 21 C.F.R. § 310.3(h)(1)-(2) (2015).

121. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDANCE FOR FDA STAFF AND INDUSTRY 3 (2002) [hereinafter 2002 CPG].

122. *Id.* at 3.

123. *Id.* at 3-4.

124. *Id.*

125. NAT’L ASS’N OF BDS. OF PHARMACY, MODEL STATE PHARMACY ACT AND MODEL RULES OF THE NATIONAL ASSOCIATION OF BOARDS OF PHARMACY § 201 (2012), [MODEL STATE PHARMACY ACT hereinafter Model State Pharmacy Act] [www.nabp.net/publications/model-act](http://www.nabp.net/publications/model-act); *see, e.g.*, MO. CODE REGS. tit. 20 § 2220-1.010 (2014).

agency's resources and people.<sup>126</sup> Traditionally, SBOPs are responsible for overseeing the licensing of pharmacists, technicians (if applicable), pharmacy interns, pharmacies, wholesalers, and manufacturers of drugs within their state.<sup>127</sup> They are also responsible for investigating complaints or suspicious activities of pharmacy professionals or facilities and employ inspectors and other support staff to fulfill these duties.<sup>128</sup>

SBOPs are usually focused on policing the professionals and facilities within their jurisdiction since the FDA has more authority over the goods a pharmacy sells, but less as to how they are sold and dispensed by a pharmacist.<sup>129</sup> The compounding of medications, which is expressly described in the state's pharmacy practice act also grants the state boards authority to regulate compounders and prescriptions being dispensed within their borders.<sup>130</sup> Moreover, it is understood that the FDA relies on state boards "to have primary responsibility for the day-to-day oversight of state-licensed pharmacies that compound drugs in accordance with [traditional practices]."<sup>131</sup> However, some SBOPs may not be as equipped as others to handle the intricacies of numerous compounding inspections. Budgets for SBOPs can vary greatly, and employment of inspectors and timely action depends on legislative allocations and the SBOP's ability to respond to complaints.<sup>132</sup> Because of such limited resources, states are generally slow to identify, act on, or follow up with bad actors in the profession as evidenced by the lack of follow up in the case of NECC.<sup>133</sup>

SBOPs are not entirely without guidance when it comes to compounding and inspection issues. The National Association of Boards of Pharmacy

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126. CONGRESSMAN MARKEY ET AL., STATE OF DISARRAY: HOW STATES' INABILITY TO OVERSEE COMPOUNDING PHARMACIES PUTS PUBLIC HEALTH AT RISK 30 (2013), [www.markey.senate.gov/imo/media/doc/State%20of%20Disarray%20Compounding%20Report.pdf](http://www.markey.senate.gov/imo/media/doc/State%20of%20Disarray%20Compounding%20Report.pdf).

127. MODEL STATE PHARMACY ACT, *supra* note 125, at § 213(a)(1); *see also* Missouri Pharmacy Practice Act, Mo. Rev. Stat. § 338 (2015) (using Missouri as an example of a state pharmacy practice act).

128. MODEL STATE PHARMACY ACT, *supra* note 125, at § 213(a)(12); Mo. Rev. Stat. § 338 (2015).

129. *See generally* Thompson v. W. States Med. Ctr., 535 U.S. 357, 360 (2002) (inferring that historically, FDA action has largely been limited to pirate manufacturers of compounded products).

130. *See e.g.*, MODEL STATE PHARMACY ACT, *supra* note 125, at § 213(a)(9).

131. *Compounding and the FDA*, *supra* note 14.

132. OFFICE OF EVALUATION & INSPECTIONS, STATE DISCIPLINE OF PHARMACISTS 3 (1990).

133. *Id.*; Toni Clark & Sharon Begley, *Insight: Red Flags Ignored For Years at Firm In Meningitis Crisis*, REUTERS (Oct. 26, 2012), [www.reuters.com/article/us-usa-health-meningitis-necc-idUSBRE89P12N20121026](http://www.reuters.com/article/us-usa-health-meningitis-necc-idUSBRE89P12N20121026). The Massachusetts Board of Pharmacy issued warning letters, as did the FDA in 2006, however it failed over the next three years to adequately follow up with NECC to ensure the facility's compliance with the pharmacy practice statutes and federal guidelines. *Id.*

(NABP) does its best to help minimize these variances among states by developing and updating a “Model State Pharmacy Act” and publishing newsletters helping SBOPs and pharmacists stay updated and focused on potential problem areas in regulation.<sup>134</sup>

Yet with the model act and newsletters, there is still a patchwork of regulatory inconsistencies and adoption of the model act can vary from state to state. States that do adopt changes to their pharmacy practice acts may do so at varying paces, thus lagging legislatures may cause further variance of pharmacy regulation from state to state. Examples of these variances exist in classification systems of pharmacies. Some states, like Missouri, require any pharmacy utilizing bulk ingredients to compound a medication to be registered and possess either a Class D (non-sterile product) or Class H (sterile product) Missouri pharmacy license.<sup>135</sup> Other states, like Pennsylvania, have no classification or licensing system required to compound medications, sterile, or non-sterile compounds under their regulations,<sup>136</sup> while other states, like Florida and Ohio, have placed disclosure requirements on facilities in the past years.<sup>137</sup> Furthermore, with the ease of shipping prescription medications, some states have tried to require a pharmacy to obtain a license to ship prescription products to patients in their state.<sup>138</sup> This requirement may allow for SBOPs to potentially track where prescription medications are coming from in their state, however, there is no reliable way for them to enforce this policy, especially with pharmacies that reside many states away, right on borders, or those just ignoring state laws.

States and the FDA have led two very different paths in regulating and defining acceptable compounding practices for the pharmacy profession. Inconsistent standards, challenges of enforcement authority, and bad actors such as NECC reaffirm the need for compounders and enforcement agencies to have clear guidelines on compounding from legislators. However, past attempts to clarify these similar issues have hit many historical bumps, so the question remains as to just how effective could new legislation be in regulating compounding and ensuring patient safety?

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134. See MODEL STATE PHARMACY ACT, *supra* note 125.

135. MO. CODE REGS. ANN. tit. 20 § 2220-2.020 (2013).

136. See 27 PA. CODE § 27.18 (2012).

137. *Sterile Compounding Permit*, FLA. BOARD PHARMACY (2016), <http://floridaspharmacy.gov/licensing/sterile-compounding-permit/>; *Compounding in Ohio*, ST. OHIO BOARD PHARMACY, <https://www.pharmacy.ohio.gov/Documents/Pubs/Special/Compounding/Compounding%20in%20Ohio.pdf> (last updated Oct. 28, 2015).

138. KY. REV. STAT. ANN. § 315.0351 (West 2007); see also OHIO REV. CODE ANN. § 4279.54 (West 2014).

## V. THE “NEW REGULATION” OF COMPOUNDING – THE DRUG QUALITY AND SECURITY ACT

The failure of the MSBP and the FDA in preventing the NECC tragedy demonstrated that agencies and legislatures needed to refocus regulatory efforts of pharmaceutical compounding after almost ten years in the shadows. Mass publicity of the unsanitary conditions, lack of patient prescriptions, and mass marketing scheme, elevated the epidemic to a top concern of law makers and labeled it as a public health disaster.<sup>139</sup> However, even in spite of the NECC tragedy, many immediate attempts to regulate compounding by stricter laws have stalled or ultimately failed passing in state and federal legislatures.<sup>140</sup> As a result, Congress attempted to once-and-for-all clarify FDA oversight of compounding pharmacies and more importantly to ensure that the FDA could take swift action to combat compounds that were not made in accordance with relevant standards of practice.

### A. Federal Regulation—Outsourcing Facilities

While patients continued to present with symptoms and suffer side effects of meningitis as a result of the NECC steroids,<sup>141</sup> U.S. Congressman Fred Upton of Michigan, whose district had three of the nineteen NECC related deaths in Michigan,<sup>142</sup> introduced the DQSA to the U.S. House of Representatives on September 27, 2013.<sup>143</sup> The DQSA set forth new clarifications and additional regulations of compounding.<sup>144</sup> The DQSA passed the House on September 28, 2013, and then quickly passed the Senate without amendment on November 18, 2013.<sup>145</sup> President Obama signed the DQSA on November 27, 2013, as Public Law 113-54.<sup>146</sup>

The DQSA amended the FDCA by “protect[ing] traditional pharmacies and clarify[ing] laws related to human drug compounding.”<sup>147</sup> The DQSA

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139. Press Release, House Energy & Commerce Comm., Upton Introduces H.R. 3204, the Drug Quality and Security Act, in Response to Deadly Meningitis Outbreak (Sept. 27, 2013), <http://upton.house.gov/news/documentsingle.aspx?DocumentID=351595>.

140. See generally *2014 State Compounding Legislative Tracker*, INT’L ASS’N COMPOUNDING PHARMACISTS, [http://c.ycdn.com/sites/www.iacprx.org/resource/resmgr/Compounding\\_Stateside/IACP\\_Weekly\\_Summary\\_of\\_State.pdf?hhSearchTerms=%222014+and+state+and+compounding+and+legislation+and+tracker%2](http://c.ycdn.com/sites/www.iacprx.org/resource/resmgr/Compounding_Stateside/IACP_Weekly_Summary_of_State.pdf?hhSearchTerms=%222014+and+state+and+compounding+and+legislation+and+tracker%2) (last updated Dec. 12, 2014) (showing the progress of several compounding safety related bills, including those failing to gain approval and those stuck in committee).

141. Press Release, House Energy & Commerce Comm., *supra* note 139.

142. *Id.*

143. See Drug Quality and Security Act, *supra* note 26.

144. See *id.*

145. *Id.*

146. *Id.*

147. Press Release, House Energy & Commerce Comm., *supra* note 139.

consists of Title I relating to drug compounding and Title II relating to the Drug Supply Chain Security.<sup>148</sup> Title I clarifies Section 503A, removes the marketing prohibition from the FDAMA that was controversial, and thus has likely provided a clear and actionable definition of traditional compounding and a separate category for those to be labeled as “outsourcing facilities.”<sup>149</sup> A new section, Section 503B, relating to outsourcing facilities, was inserted after Section 503A and shifted the existing Section 503B of the FDCA to Section 503C.<sup>150</sup> Moreover, the DQSA requires the FDA to collect reports from SBOPs regarding actions against compounders through enhanced communication methods.<sup>151</sup> The DQSA took effect January 1, 2015, however, there are still some agency rules needing further action before full enforcement may occur.<sup>152</sup>

The amended Section 503B allows pharmacies to register as “outsourcing facilities” via a voluntary registration process that is subjected to enhanced regulation by the FDA.<sup>153</sup> However, the DQSA’s definition of outsourcing facilities is inadequate to protect the public because it excludes non-sterile compounds, does not require a facility to have a pharmacy license, and removes the single patient prescription requirement.<sup>154</sup> Section 503B specifically defines “outsourcing facilities” as:

a facility at one geographic location or address that . . . is engaged in the compounding of *sterile drugs* [emphasis added] . . . [that] has elected to register . . . complies with all of the requirements of [the] section . . . [furthermore] [a]n outsourcing facility is not required to be a licensed pharmacy . . . [and] may or may not obtain prescriptions for identified individual patients.<sup>155</sup>

However, the limitation to only sterile drugs under the DQSA misses an opportunity for enhanced FDA regulation of compounding and is suggestive that future FDA enforcement should not be concerned with non-sterile

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148. Drug Quality and Security Act, *supra* note 26, at tits. I, II. Title II introduces additional provisions to make drugs easier to trace (from manufacturer to patient) throughout the U.S. supply chain. *Id.* However, it will not be discussed in this paper, and, as such, the term DQSA will relate to Title I only.

149. *Id.* § 102(a).

150. *Id.*

151. *Id.* § 105(a)(1).

152. *See id.* § 503B(a)(2)(A)(i) (noting that the Secretary is to establish a list of bulk drug substances).

153. Drug Quality and Security Act, *supra* note 26, at § 503B(a)(1).

154. *Id.* § 503B(d)(4).

155. *Id.* § 503B(d)(4)-(5).

compounding—even on a large scale.<sup>156</sup> However, even with such focus, Section 503B’s registration is completely voluntary and only applicable to those “outsourcing facilities” producing sterile drugs that may be compounded with or without a patient name.<sup>157</sup> Section 503B also departs from the idea that compounders, who are generally not regarded or registered as manufacturers, may now produce sterile compounds as “mini manufacturers” for hospitals, ambulatory care centers, physician office use, etc. *without* a prescription.<sup>158</sup> As such, the DQSA gives credence to historically-labeled “pirate manufacturers” in compounding, so long as they register as an outsourcing facility and that these “new drugs” being compounded or manufactured without a patient specific prescription, would not be required to go through the approval process laid out by the 1962 Amendments.<sup>159</sup>

Instead, the registration process under the amended Section 503B provides an incentive to outsourcing facilities compounding these non-patient specific, sterile medications.<sup>160</sup> Section 503B exempts registered outsourcing facilities from violations arising under FDCA Section 502(f)(1) (misbranding),<sup>161</sup> Section 505 (new drugs),<sup>162</sup> and Section 582 (substances generally recognized as safe),<sup>163</sup> if the compounds made in these facilities are done so by or under the direct supervision<sup>164</sup> of a licensed pharmacist in a registered facility that meets the other conditions of the section.<sup>165</sup> Therefore, registration as an outsourcing facility and successful inspection by the FDA will be a “safe harbor” from violations of the aforementioned sections of the FDCA.<sup>166</sup>

The extent of how many entities producing sterile compounds and volunteering to undergo this registration is still unknown; however, it is not very likely to be widespread. There is a great amount of work and expense required prior to inspection by the FDA, especially in implementing CGMPs

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156. *Id.* Indicative of this focus on sterile drugs, the Act even further defines a “sterile drug” as “a drug that is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law.” *Id.*

157. *Id.* at § 503B(b).

158. *See* Drug Quality and Security Act, *supra* note 26, at § 503B(b).

159. 1962 Amendments, *supra* note 89, at § 102(d).

160. *See* Drug Quality and Security Act, *supra* note 26, at § 503B(a)(1).

161. *See id.*

162. *See id.*

163. *See id.*

164. *See id.* While the FDA does not define direct supervision, it is generally understood by the pharmacy profession as requiring “a pharmacist [to] be physically present in the pharmacy, or in the area where the practice of pharmacy is occurring, and provide personal review and approval of all professional activities.” OHIO ADMIN. CODE § 4729-5-01 (2014). Terms like “area” however remain vague and are open to interpretation by state inspectors. *Id.* (failing to define the term “area,” thus opening such terms up for interpretation).

165. *See generally* Drug Quality and Security Act, *supra* note 26, at § 503B(a)(1).

166. *See id.*

which are more stringent than USP standards. Furthermore, each facility has to allow for the flexibility to adapt to changing lists still yet to be promulgated by the Secretary of Health and Human Services (HHS)<sup>167</sup> and that have been repeatedly pushed back.<sup>168</sup> Moreover, several requirements that all outsourcing facilities must prove and adhere to throughout their initial and continued registration are laid out by the DQSA's Section 503B.<sup>169</sup> Missing any one part of the requirements, as written, will not afford the outsourcing facility the exemption from the aforementioned parts of the FDCA. To qualify for registration and thus the exemption, the following must be met:<sup>170</sup>

1. The outsourcing facility is in compliance with CGMPs.<sup>171</sup>
2. A drug compounded can not contain bulk drug substances unless each substance is identified on a list of established substances approved, or in shortage at the time,<sup>172</sup> by the Secretary.<sup>173</sup> The bulk substance then must be accompanied by a valid certificate of analysis, be manufactured by an establishment registered under Section 510(i),<sup>174</sup> and if applicable must comply with USP-NF or other recognized compendium monograph.<sup>175</sup>
3. All ingredients other than bulk substances used must comply with the USP, NF, or other compendium recognized by the secretary.<sup>176</sup>
4. The drug substance or other ingredient must not be withdrawn due to safety or efficacy concerns.<sup>177</sup>
5. The finished drug is not "essentially a copy" of an approved drug.<sup>178</sup>

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167. The Secretary of HHS is undergoing the formal rule making process of establishing such a list from each outside stakeholder submitting comments. *See* List of Bulk Drug Substances that May Be Used in Pharmacy Compounding; Bulk Drug Substances that May Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, 78 Fed. Reg. 72,841, 72,841-42 (Dec. 4, 2013).

168. *See* FOOD & DRUG ADMIN., PHARMACY COMPOUNDING OF HUMAN DRUG PRODUCTS UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT: GUIDANCE 5 (2015) [hereinafter 503A GUIDANCE].

169. Drug Quality and Security Act, *supra* note 26, at §§ 503B(a), 503B(b).

170. *Id.* §§ 582(a)(3)(ii), 582(a)(3)(iii).

171. *Id.* § 503B(a)(1). *See generally* 21 C.F.R. § 211 (2014). Current Good Manufacturing Practices are lists of extensive procedures designed to protect consumers from deficiencies in manufacturing processes. *Id.*

172. Drug Quality and Security Act, *supra* note 26, at § 503B(a)(2)(A).

173. *Id.*

174. 21 U.S.C. § 351(i) (2012).

175. *Id.* § 351(a).

176. *Id.* § 351(c).

177. *Id.* § 351(d)-(e).

178. Drug Quality and Security Act, *supra* note 26, at § 503B(d)(2). "Essentially a copy" is defined by section 503B as "(A) a drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) . . . , not on a list of drug shortages "at the time of compounding, distribution, and dispensing; or (B) a drug, a component of which is a bulk drug

6. The finished drug is not demonstrably difficult for compounding—as determined by a list to be published by the secretary.<sup>179</sup>
7. The facility has an appropriate risk evaluation control system in place if the drug is compounded utilizing an ingredient indicated by an FDA Risk Evaluation and Mitigation Strategies (REMS) program.<sup>180</sup>
8. The compounded drug must not be available for “wholesale” or sale by an entity other than the outsourcing facility.<sup>181</sup>
9. The drug is labeled appropriately.<sup>182</sup>

Other requirements include paying of outsourcing facility registration fees,<sup>183</sup> and ensuring that the facility is in compliance with Section 503B(b), which sets the registration and reporting standards of drugs at an outsourcing facility.<sup>184</sup> The fees mentioned by the DQSA appear in Section 744K of the FDCA, on which the FDA released guidance at the beginning of the 2015 fiscal year.<sup>185</sup> The annual registration fee is an up-front payment of \$15,000 (adjusted for inflation)<sup>186</sup> that includes registration and initial inspection.<sup>187</sup> However, on the likely chance that the outsourcing facility does not pass initial inspection and after FDA follow-up to verify that the initial deficiencies are corrected, an outsourcing facility is subject to a re-inspection fee of another \$15,000 for each subsequent inspection deemed necessary before the facility is

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substance that is a component of an approved drug or a marketed drug that is not subject to 503(b) and not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner . . .” *Id.*

179. *Id.* § 503B(a)(6)(A). The FDA has requested submissions. *See* List of Bulk Drug Substances that May Be Used in Pharmacy Compounding; Bulk Drug Substances that May Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, 78 Fed. Reg. 72,841, 72,841-42 (Dec. 4, 2013).

180. Drug Quality and Security Act, *supra* note 26, at § 503B(a)(7).

181. *Id.* An outsourcing facility may not contract with another pharmacy to become a wholesaler of sterile medications to patients or physician use. *Id.*

182. *Id.* § 503B(a)(10).

183. FOOD & DRUG ADMIN., FEES FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTIONS 503B AND 744K OF THE FD&C ACT: GUIDANCE FOR INDUSTRY 2 (2014) [hereinafter FEES 744K].

184. Drug Quality and Security Act, *supra* note 26, at § 503B(a)(10)(b).

185. FEES 744K, *supra* note 183, at 1.

186. *Id.* at 2. Amount will be \$15,000 multiplied by the inflation adjustment factor compounded each year. *Id.* The inflation adjustment factor will be set as one plus the average annual percentage in change of cost per full-time equivalent (FTE) position at FDA for three of the preceding four fiscal years, multiplied by compensation and benefits costs, plus the average percentage change in the consumer price index (CPI) multiplied by the proportion of all costs associated with the cost of an average FTE position at the FDA. *Id.* at 4-5.

187. *Id.*

in compliance with CGMPs.<sup>188</sup> For example, if a facility fails inspection the first time, and then does not appropriately remedy its deficiencies, a \$15,000 fee for a third inspection may be assessed.

Smaller businesses may have their fee reduced to \$5,000 for registration and an initial inspection, however, businesses are only eligible upon advanced submission of a written request and certification stating that the facility (1) qualifies for such reduction, and (2) the facility's sales are less than one million dollars annually.<sup>189</sup> This small business reduction also only applies to the initial/annual registration and not the re-inspection fee.<sup>190</sup> Therefore, if a re-inspection is assessed against the small business, that business will be responsible for paying the entire fee of \$15,000 for each re-inspection.<sup>191</sup>

Currently, fifty nine facilities have sought registration as an outsourcing facility,<sup>192</sup> however, this number fluctuates and has been as high as seventy-nine at times.<sup>193</sup> While some inspections (twelve) are still pending, the FDA issued a Form 483 to every single one of the facilities it has inspected to date.<sup>194</sup> This is meaningful because a Form 483 puts an outsourcing facility on notice that inspectors have found objectionable conditions, potentially including deficiencies in CGMPs, which "may constitute a violation of the [FDCA] . . . and [other] related acts."<sup>195</sup> Because all forty-seven of the inspected firms were issued Form 483s, the DQSA would not afford them full protection granted through registration because that facility was not in full compliance with CGMPs and the statute.<sup>196</sup> Therefore, until the FDA has re-inspected these facilities and found them in full compliance, these companies are still open to liability under the FDCA.<sup>197</sup> To date, though, the extent of FDA action against an outsourcing facility under the new Section 503B has been limited to a warning letter or Form 483.<sup>198</sup>

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188. *Id.* at 5. Re-inspection is assessed when the FDA has to visit the outsourcing facility beyond the initial follow up to a noted deficiency upon initial inspection. *Id.*

189. *Id.* at 6. Sales of one million dollars do not have to be related to compounding activities, rather they encompass all sales associated with the business and not limited to drugs. *Id.*

190. FEES 744K, *supra* note 183, at 6.

191. *Id.*

192. *Registered Outsourcing Facilities*, FOOD & DRUG ADMIN. (Apr. 17, 2016), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm#6>.

193. *Id.* Some registrants may have pulled their registration after unsuccessful attempts to pass inspection. *Id.*

194. *Id.*

195. *FDA Form 483 Frequently Asked Questions*, FOOD & DRUG ADMIN., <http://www.fda.gov/ICECI/Inspections/ucm256377.htm> (last visited Feb. 17, 2015).

196. Drug Quality and Security Act, *supra* note 26, at § 503B(a); *Registered Outsourcing Facilities*, *supra* note 192.

197. Drug Quality and Security Act, *supra* note 26, at § 503B(a).

198. *See Registered Outsourcing Facilities*, *supra* note 192.

Additionally, the DQSA calls for enhanced communication between SBOPs and the FDA.<sup>199</sup> The DQSA now requires the FDA to collect reports from SBOPs regarding any state actions or agency concerns individual states have about a compounding pharmacy acting outside of Section 503A.<sup>200</sup> However, this requirement has little regulatory capability and serves mainly for documentation purposes if the FDA were to take action against individual pharmacies in a certain state.

The DQSA undoubtedly addresses large-scale sterile compounders and suggests enhanced record keeping requirements on a state level, however the opportunities to address larger issues that could directly affect the efficacy of compounding regulation seem to have been passed on. While the DQSA does not miss all opportunities to effect change, it does firmly and finally establish a true definition of compounding for the FDA and state agencies, however, enforcement of the definition will likely require more than just the words included in the Act.

## VI. REGULATORY CONSEQUENCES AND OVERSIGHTS

Although the DQSA provides a much-needed system of registration for large-scale compounders, it leaves potentially dangerous regulatory oversights that could have provided a higher degree of public safety in compounded medications.<sup>201</sup> These gaps arise greatly by making the process voluntary and specific to sterile compounds, while missing the larger problem of identifying compounding pharmacies and facilities. Furthermore, the increased pressure and enhanced duties of reporting imposed on SBOPs may strain already overworked SBOPs and further exhaust tight budgets.

### A. *DQSA Does Not Identify Sterile Compounders Nationwide*

According to a report to the House Energy Committee written months before passing the DQSA, SBOPs and compounding are in a “[s]tate of [d]isarray.”<sup>202</sup> As of April 15, 2013, only two states routinely tracked the number of compounding pharmacies in their state, and, moreover, only thirteen states even knew what pharmacies were compounding sterile products.<sup>203</sup> Fixing the problems in compounding regulation requires knowledge of just how big of a problem there may be. Legislators may have failed to realize the ease of traditional retail pharmacies expanding service lines to include compounding, or even the number of new compounding pharmacies that have been opened. In a field like pharmacy, patients could suffer from the naivety of

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199. Drug Quality and Security Act, *supra* note 26, at § 105(a).

200. *Id.*

201. *See generally* CONGRESSMAN MARKEY ET AL., *supra* note 126.

202. *Id.*

203. *Id.* at 3, 17.

these emerging practices. But the DQSA does very little to aid any agency in identifying these emerging or existing compounding pharmacies for regulators. If we were to examine the compounders in the U.S., two natural types would emerge: those providing large quantities (mainly to hospitals, doctors' offices, and infusion centers) and those compounding for the general public need based on a patient specific basis. While volume of sterile compounds dispensed can vary in each category, a categorical difference arises because most "closed-door"<sup>204</sup> compounders provide products for wholesale purposes—much like the practices NECC was engaged in. But having no mandatory identification of compounding activities for these two types of pharmacies presents different difficulties to patient safety, and without mandatory identification, neither state boards nor the FDA can always accurately assess and inspect the facilities to uncover potential risks to public health.

Many large-scale compounding facilities that would register with the FDA today gear sales towards institutional clients like doctors' offices, hospitals, and ambulatory care centers. This trend holds true when examining the types of facilities that have voluntarily registered with the FDA to date, but the question arises as to why only fifty-nine facilities have registered?<sup>205</sup> Other facilities like those registered should be jumping to be labeled as an outsourcing facilities under the DQSA to take advantage of the FDCA exemptions, but many are likely not. Logic suggests that low registration could be due to reasons such as the past history of the FDA and SBOPs minimal action against these types of facilities, the facilities could not meet the CGMPs necessary (as demonstrated by the numerous issuances of Form 483),<sup>206</sup> or even because agencies were ill equipped to identify these actors,<sup>207</sup> which would allow the facilities to take their chances and slip under the regulatory radar.

Thus, creating a *voluntary registration*, regardless of the safe harbor, has been realistically inefficient in identifying and encouraging those engaging in mass-compounding to register as an outsourcing facility. Unless a facility has a lot to lose, or they are close already to complying with the heightened CGMP

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204. Eileen Beal, *Closed-door Pharmacy Provides Patients With Worry-free Process*, CRAIN'S CLEVELAND BUS., Oct. 5, 2012. "Closed door" is a term used to indicate the pharmacy generally has no "walk-in" or retail-public (where anyone can be a customer) type of business model. *Id.* Instead sales are usually done through liaisons of the pharmacy or facility direct to physicians, hospitals, or in some cases patients, etc. *Id.*

205. *Registered Outsourcing Facilities*, *supra* note 192. A breakdown of the pharmacies included on the list as of January 30, 2015 include only four pharmacies with public retail prescriptions. *Id.*

206. *Id.*

207. Massachusetts had no idea of the sterile compounding pharmacies in their state until after NECC when they received thirty-nine self-disclosures for sterile compounding pharmacies. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 11.

standards and passing FDA inspection, voluntary registration will only minimally incentivize awareness of these compounding facilities and the conditions in which they produce their products.

Apart from the outsourcing type facilities, pharmacies that provide sterile compounds mainly for the general public are also not likely to register as an outsourcing facility even if they decide they will “outsource” some amount of prescriptions each year to a doctor’s office or hospital. General public retail pharmacies provide patients with sterile compounds like preservative free vitamin injections, erectile dysfunction injections,<sup>208</sup> or fortified eye drops,<sup>209</sup> which all need to meet sterility requirements under the USP.<sup>210</sup> These compounds are made by the local independent or possibly chain drug store pharmacies, some of which may compound hundreds of sterile products a month or others just a few. However, strict adherence to USP standards may vary across pharmacies, so therefore trying to comply with heightened CGMPs would not be an incentive to register. Moreover, some compounding pharmacies lack the necessary equipment to even perform these sterile manipulations safely. Therefore, while Section 503B may be alluring to some, many general public pharmacies will likely pass on registration.

Another deterrent, besides a detailed FDA inspection, that general-public pharmacies will face to registration is the annual cost of registration under Section 503B. Most pharmacy businesses will easily exceed the million-dollar sales ceiling provision in Section 503B that would qualify the business for a reduced-fee inspection and registration fee. The average pharmacy has about three million dollars in sales a year,<sup>211</sup> and while some may argue that the pharmacy could surely afford the higher fee, the margin from three million dollars in sales may not even equate to much more than breaking even in the end.<sup>212</sup> Most pharmacies used by the general-public receive marginal

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208. See *Sterile Preparations/Injectibles*, BUDERER DRUG CO., <https://www.budererdrug.com/clinicians-corner/sterile-preparationsinjectables/> (last visited Feb. 18, 2016). Common examples of indications for which an injection would be used include: erectile dysfunction, preservative free vitamin injections, and hormone injections. *Id.*

209. *Steroid and Antibiotic Eye Drops*, MEDICINET.COM (Apr. 14, 2015), [http://www.medicinenet.com/steroid\\_and\\_antibiotic\\_eye\\_drops/article.htm](http://www.medicinenet.com/steroid_and_antibiotic_eye_drops/article.htm). Fortified eye drops are often commercial antibiotic or steroid eye drops modified to increase concentrations of active drugs for serious eye infections or inflammation. *Id.*

210. See generally <71> STERILITY TESTS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 71.

211. Nat’l Pharmacists Ass’n, *2013 NCPA Digest: Community Pharmacy in the Digital Age*, NCPA DIGEST, 2013, at 6, <http://www.ncpanet.org/docs/default-source/default-document-library/2013-ncpa-digest-sponsored-by-cardinal-health.pdf>.

212. *Id.* The average independent pharmacy has typically had three million dollars in sales in each of the last ten years at the time the DQSA was passed. See *id.* Therefore, the small business reduction would not apply, as the language indicates total sales, and thus not specific to prescriptions or even compounded medication sales only. See *id.*

reimbursements on commercially-produced (already FDA approved) medications,<sup>213</sup> have high overhead costs, and a low profit margin.<sup>214</sup> Therefore, costs associated with CGMPs and the general expense of operating a pharmacy may prohibit or discourage owners from registration of their facility under Section 503B. Adding compounding, without increasing annual fees, therefore allows these pharmacies to supplement the money they are likely losing from low commercial medication reimbursements, as often compounds are billed for cash prices and without insurance.<sup>215</sup>

Therefore, because of the low ceiling for a small business exemption that is easily exceeded, the high costs to voluntary registration, and an overall lack of uniform requirements for identification imposed by many states, most of the general-public pharmacies engaging in sterile compounding will simply not register or will try to “fit” within the 503A exemption. Because of the aforementioned reasons that DQSA provided no mandatory process to identify sterile compounders or compounders in general, it may do little to ensure that stricter standards of compounding (USP or CGMPs) will be followed nationwide.

#### B. Failure in Not Including Non-Sterile Compounds

The DQSA’s silence regarding non-sterile compounds may be a critical oversight that allows for other compounding tragedy. Non-sterile compounds may be just as dangerous as sterile compounds when wrongfully prepared.<sup>216</sup> Non-sterile compounds containing ingredients with narrow therapeutic indices,<sup>217</sup> dangerous properties, short stabilities, and those with complex pH requirements,<sup>218</sup> are commonly made across the country and often include

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213. *See id.* at 7.

214. *See id.*

215. *See generally* Lisa Causey, *Nuts and Bolts of Pharmacy Reimbursement: Why It Should Matter To You*, U. HOUS. HEALTH L. PERSPECTIVES (2009), [http://www.law.uh.edu/healthlaw/perspectives/2009/\(LC\)%20Pharmacy.pdf](http://www.law.uh.edu/healthlaw/perspectives/2009/(LC)%20Pharmacy.pdf).

216. *See* Boodoo, *supra* note 34, at 227.

217. 21 C.F.R. § 320.33(c) (2015). A narrow therapeutic index drug is a drug in which “there is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or have less than a 2-fold difference in the minimum toxic concentrations and the minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring.” *Id.*

218. *See* Tommy Andersson et al., *Pharmacokinetics of Orally Administered Omeprazole in Children*, 95 AM. J. GASTROENTEROLOGY 3101, 3101 (2000). Omeprazole (brand: Prilosec™) a common gastric reflux medication for infants, requires a specific pH not less than 7.8 to be effective at neutralizing acid in the stomach, or drug degradation can occur before effect is realized. LAWRENCE A. TRISSEL, *TRISSEL’S™ STABILITY OF COMPOUNDED FORMULATIONS* 359-363 (5th ed. 2012). Omeprazole, however, is not commercially manufactured in liquid form and compounders nationwide make this suspension daily. *Id.*

hormone, pain, and pediatric medications.<sup>219</sup> For instance, imagine if an individual ingested a capsule containing nearly three times more than the prescribed and labeled amount (i.e., 300% potency) of thyroid medication,<sup>220</sup> he or she could experience cardiac arrest or other side effects from overdosing. Similarly, if a patient received an antibiotic liquid of vancomycin<sup>221</sup> that was not stored properly or sat on the shelf for too long, the antibiotic may be ineffective at treating serious bacterial diseases that result in life-threatening conditions.<sup>222</sup> These are just a few of the mistakes posing serious risks to patient safety that could occur in the process of making non-sterile compounds.

Not including non-sterile compounders that act as “outsourcing type facilities” in the DQSA’s registration may cause these facilities to continue their current outsourcing practices without stricter scrutiny. Although the DQSA reiterates a prohibition on outsourcing (or wholesaling) to physicians’ offices, some SBOPs still permit the practice on a limited basis thus creating a rift between state and federal law.<sup>223</sup> Therefore, compounders are continuing to roll the dice in their practice of wholesaling non-sterile “office use only” compounds, potentially without enhanced safeguards required.<sup>224</sup> Physicians only further incentivize this behavior because they are in constant need of ointments, creams, and other compounded medications, which can be

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219. <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS, U.S. PHARMACOPEIAL CONVENTION, *supra* note 17, at 1, 4-5.

220. Dosages of thyroid medications are often measured in micrograms and titrated slowly due to side effects associated with overdosing a patient. *See generally Hypothyroidism In-Depth Report*, N.Y. TIMES, <http://www.nytimes.com/health/guides/disease/hypothyroidism/print.html> (last visited Jan. 23, 2016). Millions of patients in the U.S. take a thyroid medication known as Synthroid, however, some patients need higher quantities of the active drug, or are allergic to fillers in the commercially manufactured tablets which often contain dye. *Id.*

221. *See Vancomycin*, DRUGS.COM, <http://www.drugs.com/vancomycin.html> (last revised Mar. 27, 2014). Compounded vancomycin suspensions are often used for the treatment of a bacteria, *Clostridium difficile*, which causes life-threatening inflammation of the colon. *Id.* Vancomycin is available as an FDA approved drug in capsule form, but due to the high costs of capsules, some prescription insurance companies do not cover the medication, or require the patient to get a compounded form of the drug. *Id.*

222. *Vancomycin Hydrochloride*, PHARMACOPEIA ONLINE (2013), [http://www.uspbpep.com/usp31/v31261/usp31nf26s1\\_m87760.asp](http://www.uspbpep.com/usp31/v31261/usp31nf26s1_m87760.asp) (last visited Jan. 22, 2016); *see also* <1> INJECTIONS, U.S. PHARMACOPEIAL CONVENTION, USP38-NF33, 65 (U.S. Pharmacopeial Convention 2015) (describing standards for storage of injection medications).

223. *E.g.*, ST. OHIO BOARD PHARMACY, *supra* note 137 (showing that a pharmacist is allowed to compound a commercially unavailable medication).

224. *See* OHIO ADMIN. CODE § 4729-16-07 (2016); ST. OHIO BOARD PHARMACY, *supra* note 137. Office-use only compounds are those purchased by the physician and administered directly to a patient in-office. *See generally* OHIO ADMIN. CODE § 4729-16-07. In practice, the compound does not leave the office nor is it given to the patient for continued treatment. *Id.*

customized to their preferences, to perform tests and treatments in office and at a premium.<sup>225</sup>

Therefore, from a public welfare and pharmacy practitioner's perspective, leaving out non-sterile compounding does not necessarily ensure that compounding is "safer" for all. The DQSA thus fails in part because it should have been broad enough to allow a facility producing and dispensing sterile, non-sterile, or both, types of compounds without a patient specific prescription the ability to register. Including all forms of compounds would have then shifted the emphasis of the Act and its exceptions to focus on having a prescription, regardless of the type of compound and thereby minimizing the potential for another large-scale batched tragedy.

*C. Problem with Reliance on State Boards While Providing No Additional Help*

The DQSA may be viewed as an attempt to strengthen state regulation of compounding pharmacy, but it provides little means to accomplish this task. The mere creation of an enhanced method to communicate actions against compounders between SBOPs and the FDA<sup>226</sup> is simply not enough. The DQSA recognizes and supports the FDA's reliance that the SBOPs will have primary responsibility in enforcement and day-to-day oversight of pharmacies that engage in compounding,<sup>227</sup> but provides no additional resources or fees from outsourcing facilities to do so.<sup>228</sup> The FDA has also reiterated this same position after passage of the DQSA in its "expect[ation that] state boards of pharmacy . . . continue their oversight and regulation of the practice of pharmacy, including pharmacy compounding" under Section 503A.<sup>229</sup> Yet in its statement, the FDA mentions no provision of additional resources to aid SBOPs.<sup>230</sup> Furthermore, because the marketing prohibition of Section 503A (created by the FDAMA) was removed by the DQSA, Section 503A is therefore applicable in all jurisdictions.<sup>231</sup> With Section 503A in full effect, state actions should increase, although, this assumes that SBOPs have the money to initially investigate and bring actions against different facilities. Because the burden still clearly remains on the states to address compounding enforcement, but they are provided no further help from the FDA or Congress

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225. See T.R. GOLDMAN, HEALTH AFF., REGULATING COMPOUND PHARMACIES 1-2 (2014), [http://healthaffairs.org/healthpolicybriefs/brief\\_pdfs/healthpolicybrief\\_114.pdf](http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_114.pdf).

226. Drug Quality and Security Act, *supra* note 26, at § 105.

227. See *Compounding and the FDA*, *supra* note 14.

228. See generally Drug Quality and Security Act, *supra* note 26, at §§ 105, 744K(a).

229. 503A GUIDANCE, *supra* note 168, at 3.

230. See generally *id.*

231. Drug Quality and Security Act, *supra* note 26, at § 105.

via additional resources, SBOPs may further struggle to keep the public safe from bad and negligent actors in compounding.<sup>232</sup>

## VII. POSSIBLE SOLUTIONS TO REGULATORY GAPS

Even with the shortfalls of compounding regulation, several solutions are available to help identify and enforce compounding standards across the country. However, these steps must be proactive and not reactive to avoid another tragedy similar to NECC. At the forefront, SBOPs must be the strongest advocates to bring about protection under broad compounding regulation in their state. Following one or several of the recommendations below may aid SBOPs in their continued responsibility to ensure public safety from bad actors providing compounded medications.

### A. *Pharmacies/Facilities Should Be Required to Identify Themselves as Engaging in Compounding.*

Compounding facilities should be required to register what compounding activities they are engaging in and what types of compounds they are producing. Missouri is one of only a few states that requires pharmacies to register through the utilization of a multi-class licensure system that allows the SBOP to track pharmacies on a yearly basis.<sup>233</sup> Missouri's "Class D" and "Class H" pharmacy licenses are specific to producing non-sterile and sterile drugs from bulk substances respectively.<sup>234</sup> Of the licensed pharmacies located in Missouri this year, 428 pharmacies have valid registrations for either a "Class D" or "Class H" license.<sup>235</sup> Other states, like Mississippi, require registrations to know the number of compounding pharmacies, but do not track those performing sterile compounding.<sup>236</sup> However, some states required no indication on an individual pharmacy's registration as to whether or not they perform compounding, much less sterile compounding, at the time of the DQSA.<sup>237</sup> Coupling the lack of state identification systems with the facilities identified by the DQSA's voluntary registration<sup>238</sup> indicates that there is a need to identify compounders in the U.S.

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232. Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, 79 Fed. Reg. 37,742, 37,742 (July 2, 2014).

233. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 3, 15.

234. MO. CODE REGS. tit. 20 § 2220-2.020 (2013).

235. MO. DIV. OF PROF'L REGISTRATION, *Downloadable Listing: Pharmacy*, <http://pr.mo.gov/listings-pha.asp> (last visited Jan. 21, 2016) (obtained from a spreadsheet of Missouri Board of Pharmacy License Data filtered licenses to include class D or H).

236. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 15.

237. *Id.*

238. *Registered Outsourcing Facilities*, *supra* note 192.

To identify compounders, SBOPs could easily create an additional question regarding compounding on pharmacy or pharmacist licensing applications asking if they engage in compounding, and, if so, what type they are engaged in. The state could decide whether or not to impose fees for compounders or pharmacies, much like Missouri's classification does,<sup>239</sup> or simply use it as an identifier for their records and inspectors since outsourcing facilities require supervision by a licensed pharmacist.<sup>240</sup> As an example of this type of implementation, only months after NECC, Massachusetts requested all pharmacies to report under penalty of law whether or not they were engaging in sterile compounding.<sup>241</sup> Thirty-nine of over one thousand pharmacies identified themselves shortly thereafter.<sup>242</sup> The same could go for pharmacists or pharmacies renewing their licenses yearly or on the scheduled expiration date.

Some states have elected to change their registration process since the tragedy,<sup>243</sup> but some states have not.<sup>244</sup> If states choose not to require registration, it would be possible for the FDA to require all pharmacies to register as compounders in a national database, similar to the National Provider Identification database. This database could then be utilized by states during inspection efforts to ensure proper awareness of those engaging in compounding activities. Moreover, to help ensure accurate reporting of compounding activities, SBOPs or the FDA could seek to require management of facilities to certify where they fall under the FDCA (Section 503A or 503B), or to indicate they are not engaged in compounding at all during registration and renewal.

Fixing the problem of compounder identification would be the first and perhaps most critical step towards building effective regulation and greater patient safety, and it would come at little cost to agencies. Identification can provide state and federal inspectors the valuable awareness that may save lives and allow faster response to compounding complaints. In the near future, states

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239. MO. CODE REGS. tit. 20 § 2220-4.010 (2013). Missouri charges a licensing fee to compounding pharmacists only. *Id.*

240. Drug Quality and Security Act, *supra* note 26, at § 105.

241. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 11.

242. *Id.*

243. See, e.g., *Pharmacy Terminal Distributor of Dangerous Drugs*, ST. OHIO BOARD PHARMACY, <http://www.pharmacy.ohio.gov/Documents/Licensing/TDDD/General/Terminal%20Distributor%20Licensing%20of%20Prescriber%20Practices.pdf> (last updated Oct. 8, 2015).

244. See, e.g., *Pharmacy Application*, PENN. ST. BOARD PHARMACY, <http://www.dos.pa.gov/ProfessionalLicensing/BoardsCommissions/Pharmacy/Documents/Applications%20and%20Forms/Non-Application%20Documents/PhamrF%20-%20Central%20Processing%20Center.pdf> (last visited Feb. 18, 2016). Pennsylvania has not required identification of compounders via a separate licensing or registration system. *Id.*

should lead the push towards requiring identification or licensure for any pharmacy, facility, or maybe even pharmacists engaged in compounding.

*B. Increasing Resources for State Boards of Pharmacies (Inspections and Education of Inspectors)*

1. Inspectors and Inspections

Another flaw in the DQSA is that it does not address the patchwork of state board inspection and enforcement abilities across the U.S. It fails to realize that SBOPs need additional funding and enhanced or uniform training for inspectors if they are to effectively carry out their responsibilities and be relied on by the FDA. Therefore, to truly succeed, the FDA should find ways to facilitate and standardize compounding inspections, inspector education, and enforcement through SBOPs. NABP, an independent agency, is currently working on uniform standards that states may utilize when inspecting compounders.<sup>245</sup> But without adoption by all states, SBOPs may continue to enforce standards differently or to overlook pharmacies that may actually require a higher level of scrutiny during inspection.

To demonstrate the need for standardization and further support, two SBOPs, Missouri and Ohio, are contrasted from information detailed in the “State of Disarray” report given to the U.S. House of Representatives in November of 2012, before the passage of the DQSA.<sup>246</sup> In the report, Missouri reported 1,570 licensed in-state pharmacies (442 compounding) from the Missouri SBOP’s (MoSBOP) most recent year on file.<sup>247</sup> However, the MoSBOP only employs *eight* inspectors, which, disturbingly enough, is above the national average.<sup>248</sup> These eight inspectors completed 1,242 inspections at pharmacies and other facilities related to pharmacy practice in the state, or roughly 155 pharmacies per inspector.<sup>249</sup> However, this number indicates that inspectors did not reach about 300 pharmacies, and because a lot can change year-to-year with pharmacies, especially in the lucrative compounding market, it is important to have regular inspections. At this time, Missouri is one of few

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245. See MODEL STATE PHARMACY ACT, *supra* note 125.

246. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 14. The report was compiled from responses to a series of questions sent to SBOPs “designed to examine the degree to which individual states [were] capable of overseeing the safety of compounding pharmacy practices” and enforcement within their state. *Id.*

247. *Id.* at 16.

248. *Id.* at 19. Boards of Pharmacy in the U.S. have anywhere from one to thirty inspectors with the average being only five inspectors per state. *Id.* at 26. California has the most with thirty full time inspectors, however they have over 6,700 pharmacies licensed in state. *Id.* at 26-27. This number of licensed pharmacies furthermore, does not include other facilities they inspect regularly like wholesalers, and manufacturers in their state. *Id.* at 25.

249. *Id.* at 34.

states that maintains the special classification for compounding pharmacies, inspects them regularly, and actively follows up on non-compliance.<sup>250</sup>

In the same report, Ohio reported an estimated 2,700 pharmacies registered with no indication of how many engaged in compounding.<sup>251</sup> Ohio's SBOP employed *twenty-two* full time inspectors who performed only an estimated 1,100 inspections, or an average of fifty per inspector.<sup>252</sup> Therefore, it is estimated that around 1,600 pharmacies in Ohio were not inspected in the year prior to the survey.<sup>253</sup> This comparison illustrates the differences that exist among SBOP's inspectors and inspection capabilities. While Missouri's inspectors covered a lot of ground—they performed roughly triple the amount of inspections as Ohio—this naturally raises questions as to the level of consistency in state-by-state enforcement.

Any remedy to lax inspection levels, though, would ultimately add additional costs to SBOPs. Hiring new inspectors and paying for advanced training is not always in the budget for each state and could be created through federal match programs or solely by the FDA as an arm for enforcing Section 503A themselves. After all, insufficient follow-up was one of the main reasons the NECC tragedy occurred and why NECC continued to operate for years after being issued warning letters by the FDA and the MSBP.<sup>254</sup> Working to create more resources and inspectors will only aid the ongoing inspection and follow-up processes.

## 2. Randomized Testing

Another potential solution to increase compound quality and identify bad actors is to test randomized samples of products from compounding pharmacies. This may serve as another tool to identify those compounders not working to sufficiently minimize some of the five risks associated with compounding. To aid this task, the FDA could implement a mechanism, by means of funding or through use of their own labs, to allow state submissions of randomly collected compounding samples for analysis.

Missouri already performs testing on compounds made within the state; however, the testing is reactive in nature.<sup>255</sup> In fiscal year 2013, Missouri inspectors responded to twenty-three compounding complaints and performed potency tests on fifty-six compounded medications seized during inspections

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250. MO. BD. OF PHARMACY, ANNUAL REPORT FY 2013 20 (2013) [hereinafter MO. REPORT].

251. CONGRESSMAN MARKEY ET AL., *supra* note 126, at 35.

252. *Id.*

253. *Id.*

254. *Id.* at 9.

255. MO. REPORT, *supra* note 250, at 20.

or requested as a result of complaints.<sup>256</sup> Results found seven unsatisfactory compounds ranging in potency from 3.3% to 226.6%.<sup>257</sup> All unsatisfactory compounds were non-sterile, and five of those seven contained medications with a narrow therapeutic index.<sup>258</sup> The state then shared its analysis with each pharmacy and required pharmacies with an unsatisfactory compound to complete a “quality assurance review” of compounding practices and to provide a follow-up “corrective action plan” to the board of pharmacy.<sup>259</sup> Although the tests were reactive initially, the state was able to identify and document compounders with deficiencies and correct them.<sup>260</sup> There is no doubt the actions of the MoSBOP increased the quality of compounds produced and ensured the safety of the patients in their state.

Although randomized testing may prove expensive, the insight provided to SBOPs of possible deficiencies within a compounding facility that may be otherwise unreported or unchecked is highly useful. It is also a way for inspectors to test and validate the skills and procedures utilized by compounders before it may be too late.

### 3. Independent Accreditation

Another way to reduce strain on state inspectors could be to allow independent accreditations to serve as compound specific “inspections” in limited circumstances.<sup>261</sup> Accreditation for compounding is very labor intensive and can cost a significant amount, but does come with rewards.<sup>262</sup> Compounding accreditations are popularly used as a way for compounders to “market” and separate themselves from others in the practice.<sup>263</sup> Organizations like the Pharmaceutical Compounding Accreditation Board (PCAB)<sup>264</sup> offer a voluntary accreditation process for compounding pharmacies.<sup>265</sup> The process requires multiple and extremely thorough inspections before accreditation is obtained.<sup>266</sup> These outside agencies examine a facility’s standard operating

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256. *Id.*

257. *Id.*

258. *Id.* Active ingredients in the unsatisfactory compounds included: chloramphenicol, estriol, estradiol, progesterone, DHEA, testosterone, liothyronine, levothyroxine, and omeprazole. *Id.*

259. MO. REPORT, *supra* note 250, at 20.

260. *Id.*

261. *See* PCAB ACCREDITATION MANUAL, *supra* note 61.

262. *Id.* at 42.

263. *Id.* at 36.

264. *Id.* at 1. PCAB’s board of directors include the American College of Apothecaries, National Community Pharmacists Association, American Pharmacists Association, National Alliance of State Pharmacy Associations, International Academy of Compounding Pharmacists, National Home Infusion Association, and the United States Pharmacopeia. *Id.*

265. *Id.* at 1.

266. PCAB ACCREDITATION MANUAL, *supra* note 61, at 31.

procedures (SOPs) and scrutinize their compliance to USP guidelines much more than a typical state board inspector may necessarily do in a couple hours of inspection.<sup>267</sup> While accreditation may not make the pharmacy community immune from a repeat of NECC,<sup>268</sup> it could help to safeguard the public and identify the highest quality compounders. States may choose to never require accreditation by an outside agency, however, accreditation could be considered as a factor for future enforcement actions and regulation.

#### VIII. CONCLUSION

Prescription compounding is a dangerous and continually growing market. Large margins, high utilization, and a growing need for compounds due to drug shortages and the desire for customized medications have brought out the deficiencies in regulation. While it is still too early to tell whether the DQSA will be effective in regulating compounders and ensuring patient safety, its deficiencies leave unanswered questions as to the effectiveness of regulatory efforts. The DQSA's lack of a mandatory registration or identification system should drive SBOPs to investigate and implement regulations to identify compounding facilities within their state and to take a tougher stance in enforcement actions. However, limited SBOP resources and variances between states' regulations may stifle truly effective regulation and continue to leave patients at risk. As we move forward and public awareness of compounding regulation fades, "pirate" compounders may again look to maximize their business through manufacturer-like and other risky behaviors. Therefore, it will be vital for the FDA and SBOPs to continue promulgating regulations that effectively enforce adherence to good compounding practices set forth by the USP. Until we ensure regulations are consistently implemented, followed, and reviewed, bad actors and uneducated compounders will continue to risk the safety of patients across the country.

TYLER DINKELAKER\*

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267. *Id.* at 13.

268. Stephen Barlas, *Deaths From Contaminated Methylprednisolone Highlight Failures of Compounding Pharmacies: Less Hospital Access to Outside Vendors and More Visits From State Pharmacy Boards*, 38 PHARMACY & THERAPEUTICS 27, 28 (2013) (stating NECC was not PCAB accredited at the time of the meningitis outbreak).

\* R.Ph.; Pharm.D., St. Louis College of Pharmacy; J.D., Saint Louis University School of Law. I would like to thank Professor Kelly Dineen and Professor Robert Gatter for their guidance and insight throughout the writing process and for their encouragement that I continue analyzing the intersection of pharmacy practice and the law; the members of the *Saint Louis Journal of Health Law & Policy*, especially Paige Blumenshine, for their dedication and commitment to each and every article; and to the first pharmacists I knew, my mother and father, John & Donna Dinkelaker, for teaching me what it truly means to be a pharmacist and for their unwavering support as I continue to pursue my passions for the practice of pharmacy and law.