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The Dark Side of the Pharmaceutical Industry: A *Compound* of Issues

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I. INTRODUCTION

Upon walking into a medical facility, such as a doctor's office, the likelihood that an individual will leave with a prescription in hand is high.[1] In 2016 alone, there were approximately 4.45 billion prescriptions issued throughout the United States ("U.S."). This was a significant increase from 3.99 billion prescriptions dispensed six years earlier.[2] The Center for Disease Control and Prevention reported that between 2011 and 2014, 48.9 percent of individuals used at least one prescription medication in any given 30 day period.[3] Trending data seems to indicate that these numbers are growing.[4] In the U.S. and Canada, this excessive prescribing of medication can be attributed to several factors, including preventative healthcare, pharmaceutical marketing, and, of course, the actual treatment of a medical disease or condition.[5] With a heavy reliance on the utilization of medications, local pharmacies primarily supply federally approved medications to customers. While federally approved drugs

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[1] Troyen Brennan, *Why Are Physicians Still Prescribing High Cost Brand Name Drugs? Ask Pharma*, REAL CLEAR HEALTH (May 14, 2017), https://www.realclearhealth.com/articles/2017/05/14/why_are_physicians_still_prescribing_high_cost_brand_name_drugs_ask_pharma_110590.html; Geoffrey F. Joyce, *Physician Prescribing Behavior and Its Impact on Patient-Level Outcomes*, PUBMED (Sept. 24, 2013), http://pubmedcentralcanada.ca/pmcc/articles/PMC3782257/.

[2] *Total Number of Medical Prescriptions Dispensed in the U.S. from 2009 to 2016*, STATISTA, https://www.statista.com/statistics/238702/us-total-medical-prescriptions-issued/ (last updated 2019).

[3] *Therapeutic Drug Use*, CDC, https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm (last updated May 3, 2017).

[4] *Id*.

[5] *See* Brennan, *supra* note 1; *see also* Joyce, *supra* note 1.

meet the demands of the population,[6] some consumers face challenges in obtaining medications appropriate for specific allergies, dosages, and other needs.[7] This is where the practice of pharmaceutical compounding comes into play.

Traditional pharmaceutical compounding involves the combining of individual pharmacological ingredients with the intent to create a custom medication required by a patient.[8] Traditional compounding pharmacies may also modify commercially available drugs to fit an individual's needs.[9] On the other hand, outsourcing facilities, while also compounding drugs, differ in the respect that they do so on a much larger scale.[10] These facilities are not necessarily confined to creating personalized compounds for individuals.[11] Rather, they may provide compounds to hospitals, long-term care facilities, and other providers during drug shortages.[12]

Despite providing citizens with a necessary additional avenue to acquire medication, safety concerns regarding the general practice of pharmaceutical compounding have recently been in the spotlight.[13] In the U.S., the Food and Drug Administration ("FDA") determined that state government agencies have not done an adequate job of inspecting compounding facilities and enforcing required

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[6] *See generally* Amanda Baltazar, *What is Drug Compounding?*, VERY WELL (Feb. 4, 2017), https://www.verywell.com/what-is-drug-compounding-2663861; *see also* Thomas Wong and Gordon Joseph, *Canada's Provincial Drug Formulation System*, REGULATORY AFFAIRS PROFESSIONALS SOCIETY (Nov. 2011).

[7] *Id.*

[8] Robert J. Timko & Philip E. M. Crooker, *Pharmaceutical Compounding or Pharmaceutical Manufacturing: A Regulatory Perspective*, 18 INT'L J. OF PHARMACEUTICAL COMPOUNDING 101, 102 (2014).

[9] *Id*.

[10] *See generally* Michael Werner, *Drug Quality and Security Act Gives FDA Authority to Regulate Drug Compounding and Creates Uniform Federal Standards for Distribution*, JDSUPRA (Nov. 19, 2013), https://www.jdsupra.com/legalnews/drug-quality-and-security-act-gives-fda-47575/.

[11] *Id*.

[12] *Id*.

[13] Tim Alamenciak, *FDA Uncovers Widespread Problems at Compounding Pharmacies*, THE STAR (Apr. 12, 2013), https://www.thestar.com/news/canada/2013/04/12/fda_uncovers_widespread_problems_at_compounding_pharmacies.html.

safety precautions.[14] As noted by Jane Axelrad, associate director for policy and head of FDA's compounding oversight activities, "[i]t's really appalling what we're seeing out there."[15] Axelrad reported that FDA officials have seen unsanitary conditions and other problems at traditional compounding operations which are primarily regulated by the states.[16] Inspectors have reported such violations as dead insects, dog beds, dog feces, and hair within close proximity of sterile compounding areas that could easily result in the contamination of the drugs being produced.[17] Additionally, workers have been observed preparing sterile drug products without first covering their skin, which can lead to bacterial and particulate contamination.[18] Household coffee filters used to filter particulates, toaster ovens used for sterilization, and kitchen dishwashers and detergent used to clean sterile compounding equipment represents just a sample of the darker side of the compounding industry.[19] Similarly, Health Canada, the federal institution empowered to oversee drug safety and regulation, has discovered that compounding companies are slipping through regulatory cracks maintained by provincial/territorial regulatory bodies.[20] While both the U.S. and Canada have initiated actions to ensure consumer-safe pharmaceutical compounds, each country has taken divergent approaches to accomplish this task.

This article shall serve to explore the regulations created by the U.S.' FDA and Canada's National Association of Pharmacy Regulatory Authorities ("NAPRA") and the manner in which they affect the operation of compounding facilities. More specifically, it will evaluate how these regulations can have a negative impact on both consumer drug prices and their availability. Part II of this article will

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[14] Ed Silverman, *Safety Issues at Compounding Pharmacy Underscore Oversight Issues*, STAT (Apr. 8, 2016), https://www.statnews.com/pharmalot/2016/04/08/compounding-pharmacy-drug-safety-fda/.

[15] Kate Traynor, *Compounding Oversight a Work in Progress for States, FDA*, AM. SOC'Y OF HEALTH-SYSTEM PHARMACISTS (Mar. 9, 2016), https://www.ashp.org/news/2016/03/09/compounding_oversight_a_work_in_progress
_for_states__fda.

[16] *Id.*

[17] *Id.*

[18] *Id.*

[19] *Id.*

[20] Alamenciak, *supra* note 13.

provide a historical background regarding the delegation of regulatory jurisdiction over pharmaceutical compounding in both countries. Part III will summarize the recent federal actions taken by the U.S. and Canada to resolve compounding safety concerns. Part IV will compare the FDA's aim for a centralized regulatory scheme versus Health Canada's attempt at maintaining a decentralized regulatory regime. Part V will consider the current and future implications for drug prices and availability that may result from recent federal actions.

II. BACKGROUND

A. Pharmaceutical Compounding Regulations in the U.S. Prior to 2013

In 1938, Congress enacted the Food, Drug, and Cosmetic Act ("FDCA"), giving the FDA regulatory jurisdiction over the production of new medications.[21] However, since compounding fell under the umbrella of pharmacy practice, the FDA considered the practice outside its regulatory regime.[22] As such, individual states maintained regulatory power over licensing standards and professional practices for compounding.[23]

For over fifty years, the FDA deferred to state regulations for pharmaceutical compounding without any interference.[24] In 1992, an FDA agent reinterpreted the FDA's regulatory authority under the FDCA, changing the classification of pharmaceutical compounds to unapproved "new drugs."[25] This reinterpretation caused widespread panic within pharmaceutical communities.[26] The consequences for reclassifying compounds as "new drugs" would have made the pharmaceutical compounding practice both economically

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[21] Rebecca J. Riley, *The Regulation of Pharmaceutical Compounding and the Determination of Need: Balancing Access and Autonomy with Patient Safety*, HARVARD LAW SCHOOL (Apr. 2014), https://dash.harvard.edu/bitstream/handle/1/8852177/Riley.html?sequence=1.

[22] *Id.*

[23] *Id.*

[24] *Id.*

[25] *Id.*

[26] Riley, *supra* note 21.

and practicably infeasible.[27] If all pharmacy-compounded drugs are "new drugs," and therefore considered unlawful, they must first go through the approval process as specified by the FDA.[28] Ultimately, the U.S. Court of Appeals for the Fifth Circuit affirmed their initial position from 1938 that pharmacy-compounded drugs were not considered "new drugs"[29] requiring prior FDA approval, thereby leaving regulations over pharmaceutical compounds to state governments.[30] The implication of this new classification, although overturned, set the stage for a future power struggle between state and federal government control over pharmaceutical compounding regulations.

Without delineated state regulations for pharmaceutical companies, the difference between compounding and manufacturing seemed indistinguishable to the FDA.[31] This lack of transparency presented opportunities for pharmaceutical manufacturers to sidestep costly FDA regulations.[32] The FDA, in response, issued a Compliance Policy Guide for the "Manufacture, Distribution, and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies" to provide some clarification as to what falls under FDA regulations.[33] Although the guide failed to clearly define what constituted manufacturing, the FDA newly asserted that it had full discretion over prosecuting what it believed to be illegitimate compounding practices.[34]

In 1997, Congress passed the FDA Modernization Act ("FDAMA"), which provided some broad protections over the production of drug compounds.[35] These protections included explicit exemptions from the FDCA new drug, adulteration, and a misbrand-

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27 *Id.*
28 Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383, 389 (5th Cir. 2008).
29 *Id.*
30 Riley, *supra* note 21.
31 *Id.*
32 *Id.*
33 *Id.*
34 *Id.*
35 *Id.*

ing provision which was specifically aimed at preventing the labeling of drugs in a false or misleading manner.[36] Additionally, the FDAMA provided a specified list of requirements that pharmacies had to meet in order for a drug to be considered "compounded."[37] One of these requirements is that compounding must be limited to bulk substances that comply with the U.S. Pharmacopoeia ("USP") or the National Formulary ("NF").[38] This was Congress' first effort to provide public health protections to consumers of compounded drugs.[39] The Act also required states to enter into a memorandum of understanding with the FDA to address the inordinate amount of interstate distribution and provide state investigations for complaints.[40] This memorandum of understanding ("MOU") represents a formal agreement between the FDA and federal, state, or local government agencies; academic institutions; and other entities.[41] The MOU constitutes an understanding between the parties but is a non-binding agreement.[42] The intent of the MOU is to improve consumer protection through the utilization of collective resources.[43] Should a state fail to enter into the memorandum, pharmacies residing in that state would be limited to interstate distribution of only five percent of prescriptions dispensed by a pharmacy.[44] By creating this requirement, Congress maintained FDA regulatory jurisdiction over pharmaceutical compounding.

The FDA's authority over compounding once again expanded in 2001, after the U.S. Supreme Court decided *Thompson v. Western States Medical Center*. The Supreme Court held that restrictions on advertising, stated in a provision in FDAMA, violated the First

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[36] *Id.; Labeling Requirements – Misbranding*, FDA, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/GeneralDeviceLabelingRequirements/ucm052190.htm (last updated Oct. 27, 2017).

[37] Riley, *supra* note 21.

[38] *Id.*

[39] *Id.*

[40] *Id.*

[41] *FDA Memoranda of Understanding*, FDA, https://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/default.htm (last updated July 17, 2016).

[42] *Id.*

[43] *Id.*

[44] Riley, *supra* note 21.

Amendment.[45] These restrictions included that the prescription be unsolicited and that the providers not advertise or promote the compounding of any particular drug, class of drug, or type of drug.[46] Although the compounding industry gained advertising powers, the Supreme Court also reinstated the FDCA's new drug, adulteration, and misbranding provisions, affirming consumer protection through accurate and truthful labeling and marketing.[47] The Court reasoned that the reinstatement assisted in "[p]reserving the effectiveness and integrity of the FDCA's new drug approval process."[48]

Since the *Western States Medical Center* decision, an outbreak of meningitis stemming from an improperly compounded sterile drug prompted the FDA to once again expand its jurisdiction.[49] As a direct response to this incident, the FDA enacted the Drug Quality and Security Act in 2013.[50] As part of this Act, specific steps were outlined to design and implement an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the U.S.[51] Moreover, the Act was designed to enhance the FDA's ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful.[52]

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[45] *See* Thompson v. W. States Med. Ctr., 122 S. Ct. 1497, 1508–09 (2002).

[46] *Id.* at 1502–03.

[47] *See id.* at 1508–09.

[48] *Id.* at 1505.

[49] Rachel M. Smith et al., *Estimated Deaths and Illnesses Averted During Fungal Meningitis Outbreak Associated with Contaminated Steroid Injections, United States, 2012–2013*, 21 EMERGING INFECTIOUS DISEASES 933, 934 (June 6, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4451895/.

[50] Drug Quality and Security Act, Pub. L. No. 113-54 (2013), https://www.congress.gov/bill/113th-congress/house-bill/3204.

[51] *Drug Supply Chain Act*, FDA, https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ (last updated Nov. 28, 2017); *see also* Margaret A. Hamburg, *New Law Enhances Safety of Compounded Drugs and Protection of the Drug Supply Chain*, FDA VOICE (Dec. 2, 2013), https://blogs.fda.gov/fdavoice/index.php/2013/12/new-law-enhances-safety-of-compounded-drugs-and-protection-of-the-drug-supply-chain/.

[52] *Id.*

B. Pharmaceutical Compounding Regulations in Canada Prior to 2016

In 1920, Canada's FDA equivalent, the Federal Department of Health enacted the Food and Drugs Act to regulate the production, sale, and importation of food, drugs, cosmetic, and medical devices.[53] Additionally, by the late 1920s, the Food and Drugs Regulations were created to set the standards for the "composition, strength, potency, quality, or other property of [an] article of food or drug."[54] However, much like in the U.S., the Food and Drug Act and Regulations provided federal regulatory power over drug manufacturers but not compounding pharmacies.[55] This distinction was not clarified until 2000, when Health Canada published a policy titled "Manufacturing and Compounding Drug Products in Canada."[56] The aim of this policy was to better regulate the process federal regulators, provincial/territorial regulators, and healthcare professionals must follow when dealing with jurisdictional issues related to compounding and manufacturing.[57] The guiding principle of this policy maintained that compounding must be a legitimate part of the practice of regulated healthcare professionals and must not be used to bypass the federal drug review and approval system.[58] The adoption of this policy would enable a consistent Canada-wide approach to ensure that all products and activities are appropriately regulated.[59]

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[53] *Frequently Asked Questions – Food and Drug Regulations*, GOV'T OF CANADA (June 27, 2016), https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/frequently-asked-questions-food-drug-regulations.html; *see also* Food and Drugs Act, R.S.C. 1985, c. F-27 (Can.).

[54] *Id.*

[55] Health Products and Food Branch Inspectorate, *Policy on Manufacturing and Compounding Drug Products in Canada*, GOV'T OF CANADA (Jan. 26, 2009), https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/policy-manufacturing-compounding-drug-products.html.

[56] *Id*.

[57] *Id.*

[58] *Id.*

[59] *Id.*

In 2009, the Health Products and Food Branch Inspectorate provided additional clarification, publishing an administrative document noting the distinction between manufacturing and compounding.[60] Regulatory jurisdiction for pharmaceutical compounding was delegated to provinces/territories.[61] Health Canada reasoned that compounding is a licensed act that falls within the scope of pharmacy practice.[62] As such, any professional engaged in the compounding process must comply with individual province/territory licensing regulations.[63] With compliance being met, the risk involved in compounding falls entirely on health professionals.[64]

To the contrary, pharmaceutical companies that are deemed "manufacturers" must comply with more restrictive federal regulations.[65] In order for a company to sell a manufactured drug, Health Canada must review the product's quality, safety, and efficacy.[66] Moreover, manufactured drugs require a Drug Identification Number and/or Notice of Compliance in order to be sold.[67] These additional regulations reduce the production of dangerous or otherwise unsatisfactory drugs.[68]

Should there be any uncertainty as to whether drug production can be clearly categorized as manufacturing or compounding, a discussion between the federal government and provincial/territorial bodies takes place to make a final determination.[69] Yet, because each decision is decided on a case-by-case basis,[70] some manufacturing activity may be incorrectly categorized as compounding and thus, bypass certain safety standards. This has ultimately led to a number of large scale health issues.[71] For example, in an incident

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60 *Id.*
61 *Id.*
62 *Id.*
63 *Id.*
64 *Id.*
65 *Id.*
66 *Id.*
67 *Id.*
68 *Id.*
69 *Id.*
70 *Id.*
71 Amina Zafar*, Chemotherapy Outsourcing Done by Hospitals Across Canada*, CBC NEWS (Apr. 25, 2013), http://www.cbc.ca/news/health/chemotherapy-outsourcing-done-by-hospitals-across-canada-1.1308762.

that left 1200 patients in New Brunswick and Ontario with lower-than-expected dosages of the cancer drug Gemcitabine, hospitals in at least three Canadian provinces revealed that they outsourced their chemotherapy preparations through compounding facilities.[72] As a result, Health Canada is attempting to establish uniform safety standards that provinces/territories will be required to individually adopt and implement.[73]

III. SUMMARY OF THE CHANGES IN FEDERAL REGULATIONS FOR PHARMACEUTICAL COMPOUNDING IN THE U.S. AND CANADA

To understand how the newly implemented regulatory schemes for pharmaceutical compounding between the U.S. and Canada diverge, it is important to first carefully analyze each scheme independently.

A. U.S. Drug Quality and Security Act

When a New England pharmaceutical compounding company in Framingham, Massachusetts produced a tainted steroid medication that resulted in a deadly meningitis outbreak, the FDA made the decision to intervene.[74] The outbreak led to 64 deaths and 751 non-lethal injuries.[75] As a direct response to this incident, the FDA created and enacted the Drug Quality and Security Act.[76] The Drug Quality and Security Act amended the Food, Drugs, and Cosmetics Act ("FDCA"), granting the FDA additional authority to regulate

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[72] *Id.*

[73] *Model Standards of Pharmacy Compounding of Non-Hazardous Sterile Preparations*, NAPRA (Nov. 1, 2016), https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous_Sterile_Preparations_Nov2016_Revised_b.pdf.

[74] Rachel M. Smith et al., *Estimated Deaths and Illnesses Averted During Fungal Meningitis Outbreak Associated with Contaminated Steroid Injections, United States, 2012–2013*, 21 EMERGING INFECTIOUS DISEASES 933, 934 (June 6, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4451895/.

[75] *Multistate Outbreak of Fungal Meningitis and Other Infections – Case Count*, CTR. FOR DISEASE CONTROL AND PREVENTION (Oct. 30, 2015), https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html.

[76] Drug Quality and Security Act, Pub. L. No. 113-54 (2013).

the manufacturing of sterile pharmaceutical compounds.[77] Specifically, Section 503A of the FDCA was amended to regulate traditional compounders.[78] The Drug Quality and Security Act also implemented a new provision, Section 503B, to regulate larger outsourcing drug facilities.[79]

Section 503B allows compounders to voluntarily register as an outsourcing facility, which provides exemptions from FDA approval and labeling requirements.[80] In addition, registering as an outsourcing facility allows for the compounding of drugs without patient-specific prescriptions.[81] While it would seem that most companies would be disposed to register as an outsourcing facility, there are a considerable number of disadvantages. Outsourcing facilities are required to pay an FDA imposed annual registration fee of over $15,000.[82] The compounder is then subjected to federal inspections on a "risk-based" schedule.[83] Due to the FDA's extremely strict regulations, registered outsourcing facilities may be required to pay reinspection fees of over $15,000 if noncompliance is identified.[84] Additionally, outsourcing facilities must also comply with the U.S. Food and Drug Administration's Current Good Manufacturing Prac-

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[77] *Id.*

[78] *Examining Implementation of the Compounding Quality Act*, U.S. FOOD AND DRUG ADMIN. (Jan. 30, 2018), https://www.fda.gov/NewsEvents/Testimony/ucm594297.htm.

[79] *Information for Outsourcing Facilities*, U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm. (last visited Mar. 18, 2019).

[80] *Id.*

[81] *Information Concerning Outsourcing Facilities Registration*, U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm389118.htm. (last visited Mar. 18, 2019).

[82] *Human Drug Compounding Outsourcing Facility Fees,* U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/ForIndustry/UserFees/HumanOutsourcingFacilityUserFee/default.htm. (last visited Mar. 18, 2019).

[83] *Id.*

[84] *Id.*

tice ("CGMP") regulations when producing pharmaceutical compounds.[85] The CGMP requirements utilize the same strict regulations used by the FDA for approving drugs.[86] Systems must be put into place to assure proper design, monitoring, and control of manufacturing processes and facilities.[87] However, adherence to the CGMP regulations, while assuring the identity, strength, quality, and purity of the drug,[88] drives production costs up.[89] This is further exacerbated by the expense of extensive monitoring, documentation, and reporting.[90]

Should the compounding facility opt not to register as an outsourcing facility, it will be governed by 503A and state regulations.[91] While quality assurance standards are similar to those required in 503B, the individual prescription mandate in 503A prevents traditional compounding pharmacies from compounding products in large quantities.[92] Section 503A limits traditional compounding pharmacies to stocking no more than a 30-day supply of any specific compounded drug.[93] This can be problematic as pharmacists must rely on past transactions with consumers as a measure

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[85] *Information for Outsourcing Facilities*, *supra* note 79.

[86] *Facts About the Current Good Manufacturing Practices (CGMPs),* U.S. FOOD AND DRUG ADMIN., https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm. (last visited Mar. 18, 2019).

[87] *Id.*

[88] *Id.*

[89] *See Stricter Drug Compounding Regulations Complicate Ophthalmology Care*, HEALIO (Oct. 10, 2017), https://www.healio.com/ophthalmology/regulatory-legislative/news/print/ocular-surgery-news/%7B820dbc2e-6e7c-48d7-b7a3-01e75097f434%7D/stricter-drug-compounding-regulations-complicate-ophthalmology-care?page=1.

[90] *Id.; see generally Center for Drug Evaluation and Research: Outsourcing Facility Information*, FDA (Sept. 2017), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM577334.pdf.

[91] *Examining Implementation of the Compounding Quality Act*, *supra* note 78.

[92] *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry,* FDA (Dec. 2016), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/
Guidances/UCM496286.pdf.

[93] *Id.*

to predict the quantities of each drug necessary to meet future demand.

With a higher cost of production and smaller supply of products, traditional compounding pharmacies may be forced out of the market. Furthermore, with the FDA encouraging state enforcement initiatives, traditional compounding pharmacies risk being fined for producing drugs in excess due to innocent or incorrect calculations for future demand.

B. Canada's Model Standards for Pharmacy Compounding

Similar to the U.S., a health crisis resulted in the restructuring of drug compounding regulations in Canada. After the 2013 incident in which 1,200 people in Ontario and New Brunswick received lower-than-intended doses of chemotherapy,[94] Ontario amended provincial regulations to prevent this type of incident from being repeated.[95] Canada clearly needed higher and uniform standards for compounding drugs.[96] As a result, the NAPRA instituted the Model Standards for Pharmacy Compounding.[97] The Model Standards provide the *minimum* requirements to be applied in each province/territory.[98] It is important to note that these Model Standards are comprised of three phases implemented over a four year period of time.[99] The initial 2016 release of these national standards for compounding preparations is scheduled to be fully phased in by 2021.[100] Canadian pharmaceutical compounders will be encouraged to follow the four-year phased in approach to ensure they meet all requirements by

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[94] Zafar*, supra* note 71.

[95] *See generally* Jake J. Thiessen, *A Review of the Oncology Under-Dosing Incident*, ONTARIO MINISTRY OF HEALTH AND LONG-TERM CARE (July 12, 2013), http://www.health.gov.on.ca/en/public/programs/cancer/drugsupply/docs/report_thiessen_oncology_under-dosing.pdf.

[96] *See id.*

[97] *See id.*

[98] Bob Nakagawa, *125th Anniversary Conference and Gala: The Future of Pharmacy*, C. OF PHARMACISTS OF BRIT. COLUMBIA (Sept. 17, 2016), http://library.bcpharmacists.org/5_Programs/5-3_PDAP/5197-CPBC125_PowerPoint.pdf.

[99] *Implementing the New Model Standards For Pharmacy Compounding*, C. OF PHARMACISTS OF BRIT. COLUMBIA, http://www.bcpharmacists.org/compounding (last visited Mar. 25, 2019).

[100] *Id.*

May 2021, when the new bylaws become fully effective.[101] Should any compounding manufacturer repeatedly fail to meet these standards, a decision will have to be made regarding permanent termination of sterile compounding preparation.[102]

The NAPRA has released the three subsections for Model Standards for Pharmacy Compounding.[103] The three subsections consist of Model Standards for Non-Hazardous Sterile Preparation, Hazardous Sterile Preparations, and Non-Sterile Preparations.[104] With consideration to commercial compounding, the NAPRA has implemented stricter regulations regarding personnel handling and supervision of the production of compounded drugs; policies and procedures; facility design and required equipment; and general maintenance logs.[105] As an example, the Model Standards specify more stringent requirements depending on the complexity and risk of the compounding activity, the use of hazardous products in the production, and workflow.[106]

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[101] *Id.*

[102] *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), http://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_Hazardous_Sterile _Preparations_Nov2016_Revised_b.pdf.

[103] *Id.*; *see also Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), NAPRA, https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_ Preparations_March2018_FINAL.pdf.

[104] *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), http://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_Hazardous_Sterile _Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), NAPRA, https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous _Sterile_Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), NAPRA, https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf.

[105] *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations, supra* note 102.

[106] Nakagawa, *supra* note 98.

IV. CENTRALIZED VERSUS DECENTRALIZED REGULATORY FRAMEWORKS

A. State Oversight of Compounding Pharmacies

With the meningitis outbreak instilling panic within the general population in 2012, the U.S. federal government began investigating compounding pharmacies searching for safety violations.[107] While the FDA has issued warnings and recommendations identifying specific safety violations, the identified compounders and states refuse to accept the FDA as having ultimate authority in regards to pharmacy practice.[108] Although the Drug Quality and Security Act allows the FDA to inspect facilities and enforce regulations, the overlap between state and federal regulations, in addition to the disagreements between regulators, has resulted in confusion and a lack of accountability.[109]

State regulations, not being as rigorous as FDA regulations, have become the crux of ineffective government regulation.[110] An analysis by PEW Charitable Trusts, a public policy organization, determined that approximately only half of the states require compounding pharmacies that produce sterile medications to fully comply with recognized quality standards.[111] Furthermore, the PEW Charitable Trust states that there is great variability between the breadth of USP 797 requirements, which are the recognized and accepted quality standards, and enforcement between states.[112] "Regarding compounding inspector qualifications, only 70% of the states required a pharmacist license, only 60% required prior experience within a pharmacy, and only 58% required training on applicable USP standards."[113] It is an alarming issue that twenty-eight out of forty-three

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[107] Jacque Wilson, *Meningitis Outbreak: What is a Compounding Pharmacy?*, CNN (Sept. 22, 2016, 5:26 PM), http://www.cnn.com/2012/10/11/health/compounding-pharmacies-explainer/index.html.

[108] Silverman, *supra* note 14.

[109] *Id.*

[110] *Id.*

[111] *Id.*

[112] Joseph Gulfo, *Pharmaceutical Compounding: The FDA is Not the Problem*, FORBES (Aug. 26, 2016), https://www.forbes.com/sites/realspin/2016/08/29/pharmaceutical-compounding-the-fda-is-not-the-problem/#72d6ef978df8.

[113] *Id.*

respondents to the PEW survey did not require specialized training in the compounding of sterile medication.[114]

Discrepancies between the FDA and the Texas State Board of Pharmacy, in regulating compounding pharmaceutical manufacturers, illuminates the potential conflicts and confusion between the two regulatory schemes.[115] In 2016, the FDA "uncovered multiple egregious, life-threatening problems in a compounding pharmacy's process for making sterile drugs."[116] However, the FDA remains powerless to force the compounder to abide by any safety recommendations.[117] In response to the FDA's allegations along with Public Citizen's, a consumer advocacy group, plea to suspend the compounder's license, the Texas State Board of Pharmacy sent its own inspector to investigate the matter.[118] The state inspector determined that the compounder, IV Specialty, was properly abiding by state regulations and that the public was not in any imminent danger.[119] As such, the Texas State Board of Pharmacy refused to halt the compounder's production, issue a recall of drugs manufactured and delivered, or suspend the compounder's license as recommended by the FDA and Public Citizen.[120]

Apart from the varying quality standards between states, sixty percent of states of the forty-three responding states to the PEW survey do not require compounding pharmacies to track and report adverse events.[121] Additionally, compounding activity in sixteen states is completely unsupervised by state regulators.[122] Of the forty-three responding states, only fifty-three percent actually conduct annual routine inspections of compounding facilities creating sterile drugs.[123] Should any safety issue be identified during the routine annual inspection, a written response from the pharmacy describing how the issues were remediated would be required.[124] However,

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114 *Id.*
115 Silverman, *supra* note 14.
116 *Id.*
117 *Id.*
118 *Id.*
119 *Id.*
120 Silverman, *supra* note 14.
121 Gulfo, *supra* note 112.
122 *Id.*
123 Silverman, *supra* note 14.
124 *Id.*

only two-thirds of the surveyed states conduct a follow-up inspection to ensure compliance.[125] It is this lack of accountability that results in egregious violations and provides the potential for the distribution of hazardous drugs.

The Pharmacy Compounding Accreditation Board (PCAB) assesses pharmacies that compound medication, ensuring their compliance with U.S. Pharmacopeial Convention guidelines, which reduces safety risks.[126] However, compounding pharmacies are not required by states to be accredited by the PCAB, thereby removing a necessary level of protection for public health.[127]

This variation in state oversight has raised questions regarding state regulators' ability to protect public health and has prompted Congress to consider granting the FDA even more regulatory authority over the compounding industry.[128]

B. U.S. FDA's Aim Towards Centralized Regulation for Compounding Drugs

The lack of specificity within sections 503A and 503B of the Compounding Quality Act has left the door open for considerable misinterpretation.[129] The main issue is that state laws and regulations are not aligned with federal laws and regulations.[130] States vary on how they define an outsourcing facility and therefore, may fail to properly recognize and report an outsourcing facility to the FDA.[131] New York, for example, has updated statutes and regulations to include a definition and category for outsourcing facilities.[132] Other states, however, categorize outsourcing facilities with compounding pharmacies, manufacturers, or distributors, which allows these

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125 *Id.*

126 *Compounding Pharmacy Accreditation*, ACCREDITATION COMMISSION FOR HEALTH CARE, https://www.achc.org/compounding-pharmacy.html (last visited Mar. 18, 2019).

127 *Id.*

128 Gulfo, *supra* note 112.

129 Silverman, *supra* note 14.

130 *Best Practices for State Oversight of Drug Compounding*, PEW CHARITABLE TRUSTS (Mar. 2016), http://www.pewtrusts.org/~/media/assets/2016/02/best_practices_for-state_oversight_of_drug_compounding.pdf.

131 *Id.*

132 *Id.*

states to maintain control over their outsourcing facilities.[133] Because Congress, in the creation of section 503B, did not mandate that outsourcing facilities register with the FDA, the FDA lacks effective regulation.[134] This lack of control allows for safety violations by compounding facilities, causing public health issues.[135]

While the FDA attempts to entice compounders to register as an outsourcing facility by providing incentives, including bypassing the prescription requirement in 503A, state regulators negate these incentives.[136] As a number of states have no specific guidelines to handle 503A federal violations, they ultimately permit traditional compounding pharmacies to compound without individual patient prescriptions.[137] Currently, nine states have no intent to discipline pharmaceutical manufacturing violators or require these compounding pharmacies to register as outsourcing facilities with the FDA.[138] Once again, accountability seems to be absent. As such, only 73 out of 1,500 compounding pharmacies have registered as of December 8, 2017.[139]

While the FDA has the authority to take legal action against sterile compounding pharmacies that are allegedly conducting unsafe practices, it has rarely done so and remains cautious about overstepping state authority.[140] Furthermore, although the FDA has been aggressively inspecting compounding pharmacies, it relies on communication with state regulators regarding serious adverse events and quality problems reports.[141] As noted above, with sixty-three percent

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133 *Id.*

134 *Id.*

135 *Best Practices for State Oversight of Drug Compounding*, PEW CHARITABLE TRUSTS (Mar. 2016), http://www.pewtrusts.org/~/media/assets/2016/02/best_practices_for-state_oversight_of_drug_compounding.pdf.

136 Silverman, *supra* note 14.

137 *Id.*

138 *Id.*

139 *Registered Outsourcing Facilities*, FDA (Dec. 8, 2017), https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm.

140 Silverman, *supra* note 14.

141 *FDA Implementation of the Compounding Quality Act*, FDA (Sept. 9, 2017), https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm375804.htm.

of forty-three states not requiring compounders to track and report adverse events, the FDA has little knowledge and is therefore, limited in its ability to protect public health.[142]

With ineffective state oversight over compounding pharmacies and enforcement of the Drug Quality and Security Act, the FDA has requested greater jurisdiction over sterile compounded drugs.[143] Moreover, the Biotechnology Innovations Organization ("BIO"), The Pharmaceutical Research and Manufacturers of America ("PhRMA"), PEW Charitable Trusts and other groups sent letters urging Congress to provide the FDA with additional oversight authority over drug compounders.[144] These organizations stress that "[i]f [the] FDA is not permitted to maintain that line between traditional compounding and outsourcing facilities, patients are put at risk, states and compounding pharmacies will not have clear regulatory guidance, and the lessons of the national meningitis outbreak will have been forgotten."[145]

Fairleigh Dickinson University School of Pharmacy and Health Sciences has published a list of ten recommendations to improve the quality and ensure the safety of compounded drugs. The top three recommendations provide the FDA with additional authority over facilities producing sterile compounds. The three are as follows:

1. Congressional legislation removing ambiguity from provisions of section 503A and empowering the FDA to enforce 503A.[146]

2. Congressional legislation that requires outsourcing facilities to register with the FDA, thereby, mandating operations under CGMP requirements. Such action will allow inspection of such facilities to be governed by the FDA (rather than pharmacy licensing boards), which has the potential to drive closure of the sterile compounding facilities not in compliance.[147]

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142 Gulfo, *supra* note 112.

143 *Id.*

144 Zachary Brennan, *BIO, PhRMA, and Others Urge Further FDA Clarity on Drug Compounding*, REGULATORY AFF. PROF. SOC'Y. (June 14, 2017), http://www.raps.org/Regulatory-Focus/News/2017/06/14/27902/BIO-PhRMA-and-Others-Urge-Further-FDA-Clarity-on-Drug-Compounding/.

145 *Id.*

146 *MI³ Alert: Medical Innovation Impact Index – Report #8*, FAIRLEIGH DICKINSON U. (Aug. 8, 2016), https://view2.fdu.edu/Report-8_v2099d.pdf?id=18361.

147 *Id.*

3. Congressional legislation that mandates adverse event reporting and complete product labeling by all compounding pharmacies, not just registered outsourcing facilities.[148]

Although these are nothing more than recommendations, the combination of this publication and the letters sent to Congress by the BIO, PhRMA, PEW, and the other organizations illustrates the overall agreement that a more centralized regulatory framework needs to be implemented. However, with the overarching concern regarding the separation of powers, the time it may take to enact these recommendations may be well after the occurrence of another health crisis caused by unsafe compounded medications. Until Congress provides additional clarity for state and federal regulators, consumers of compounded drugs remain extremely vulnerable.

C. Proposed Legislation and State Pushback

As recently as June 2017, a new bill sponsored by Congressmen H. Morgan Griffith (R-VA) and Henry Cuellar (D-TX) was proposed that would certainly weaken consumer protection.[149] This bill would permit "traditional compounding pharmacies to distribute compounded drugs within a state without requiring an individual prescription (only a 'drug order') and without being required to follow CGMP standards as [is required by] outsourcing facilities . . . ."[150] If passed, the bill would attenuate the 2013 law that created outsourcing procedures and guidelines.[151] Compounding companies would be able to continue producing pharmaceuticals without having to register, without having to report adverse events, and without having to pay the user fees that are required with registering as an outsourcing facility.[152] More importantly, compounding pharmacies would not be required to follow CGMP standards,

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148 *Id.*

149 Preserving Patient Access to Compounded Medications Act, H.R.2871, 115th Cong. (2017); *see also* Janis C. Kelly, *Struggle to Improve Quality of Compounded Drugs Continues*, MEDSCAPE (Jan. 8, 2018), https://www.medscape.com/viewarticle/891019#vp_3.

150 Janis C. Kelly, *Struggle to Improve Quality of Compounded Drugs Continues*, MEDSCAPE (Jan. 8, 2018), https://www.medscape.com/viewarticle/891019#vp_3.

151 *Id.*

152 *Id.*

thereby saving costly expenses.[153] The potential of this bill could be catastrophic, taking the industry back to pre-2013 standards and recreating conditions that could result in outbreaks similar to that which occurred with the New England Compounding Center.[154] It is no surprise that HR2871 is strongly supported by the International Academy of Compounding Pharmacists, a trade group that donated to both Griffith's and Cuellar's political campaign.[155] With all the latitude and lower costs this bill would afford compounding companies, it would behoove these companies to support such legislation, irrespective of the potential consequences.

D. Health Canada so Far Maintains a Decentralized Regulatory Scheme

Unlike U.S. states, which take pride in considering themselves the "laboratories of democracy,"[156] Canada has been working on resolving its national unity crisis by attempting to establish provincial equality.[157] Provincial equality pertains to jurisdictional control, political representation, and economic equality.[158] Simply put, Canadian provinces are focused on making sure policies extended by the federal government and their outcomes are proportionally equal within each province. As long as a federal policy promotes uniformity, provinces are more open to accepting and enforcing that policy, especially when it is not politicized.

A recent ISMP Canada Safety Bulletin makes clear the present state of the compounding industry.[159] Canadian patients diagnosed

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153 *Id.*

154 *Id.*

155 Janis C. Kelly, *Struggle to Improve Quality of Compounded Drugs Continues*, MEDSCAPE (Jan. 8, 2018), https://www.medscape.com/viewarticle/891019#vp_3.

156 New State Ice Co. v. Liebmann, 285 U.S. 262 (1932).

157 Jennifer Smith, *The Meaning of Provincial Equality in Canadian Federalism*, QUEEN'S UNIVERSITY (1998), http://www.queensu.ca/iigr/sites/webpublish.queensu.ca.iigrwww/files/files/WorkingPapers/Archive/1998/1998-1JenniferSmith.pdf.

158 *Id.*

159 *Death Association with an IV Compounding Error and Management of Care in Naturopathic Centre*, 18 INST. FOR SAFE MEDICATION PRAC. CAN. 1, 1 (Jan. 4, 2018), https://www.ismp-canada.org/download/safetyBulletins/2018/ISMPCSB2018-01-Selenium.pdf.

with cancer have the option of choosing alternative medical approaches, including naturopathy, for treatment of their conditions.[160] In one incident, reported as recently as January 2018, a cancer patient was prescribed a tissue and wound healing formulation for postsurgical healing support.[161] The formulation was administered intravenously and contained selenium prepared by a compounding pharmacy.[162] Upon hospital discharge, after surgical excision of a cancerous tumor and subsequent to the administration of the selenium formulation, the patient began to experience hypotension, shortness of breath, and chest pain and ultimately passed away.[163] Postmortem investigations revealed that the selenium concentration in the infused formula was one thousand times greater than intended, which likely contributed to the patient's death.[164]

In another incident, after 1,200 people received lower-than-intended doses of chemotherapy in New Brunswick and Ontario,[165] Canada's federal and provincial/territorial governments became concerned with the manner in which to protect the public health from unsafe compounded drugs.[166] The Ontario Ministry of Health and Long-Term Care commissioned Dr. Jake Thiessen, a pharmacokinetic specialist, as an independent investigator to determine the cause of the incident and provide recommendations.[167] In Dr. Thiessen's report, he pointed out that the vendor who produced the doses of chemotherapy provided inter-provincial services because both New Brunswick and Ontario hospitals were affected.[168] As such, provinces and territories throughout Canada were at risk of experiencing similar incidents unless changes were made on a national scale.[169] One of Dr. Thiessen's recommendations provided that the

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160 *Id*.

161 *Id*.

162 *Id*.

163 *Id.*

164 *Death Association with an IV Compounding Error and Management of Care in Naturopathic Centre*, 18 INST. FOR SAFE MEDICATION PRAC. CAN. 1, 1 (Jan. 4, 2018), https://www.ismp-canada.org/download/safetyBulletins/2018/ISMPCSB2018-01-Selenium.pdf.

165 Zafar, *supra* note 71.

166 Thiessen, *supra* note 95.

167 *Id.*

168 *Id.*

169 *See generally id.*

NAPRA work closely with Health Canada as a means of creating the best objective standards for sterile and non-sterile product preparation within a licensing pharmacy.[170]

Dr. Thiessen's recommendation to look to the NAPRA essentially made the public health issue revolving around pharmaceutical compounding less politicized. The NAPRA is comprised of members from each province and territory that are represented on the association's board of directors.[171] With each provincial and territorial regulatory body collaborating, the NAPRA has successfully published three subsections of the Model Standards for Pharmacy Compounding to be adopted on a national basis.[172] As such, provinces and territories continue to retain full control over compounding activity, thereby resolving international unity issues and maintaining a consistent approach.

E. The NAPRA Model Standards Increase Accountability Within the Pharmacies

The NAPRA Model Standards for Pharmacy Compounding is a comprehensive set of regulations designed to increase safety standards for the preparation of sterile and non-sterile compounded drugs.[173] In contrast to the U.S., where Congress granted the FDA regulatory authority to oversee compounding pharmacies,[174] the NAPRA Model Standards preserves the authority of ensuring the

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[170] *Id.*

[171] *NAPRA Governance*, NAPRA, http://napra.ca/napra-governance (last visited Mar. 7, 2019).

[172] *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), http://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_Hazardous_Sterile _Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), NAPRA, https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous _Sterile_Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), NAPRA, https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf.

[173] *Implementing the New Model Standards For Pharmacy Compounding*, *supra* note 99.

[174] Silverman, *supra* note 14.

safe preparations of compounded drugs solely within the provincial/territorial regulatory authorities.[175] Luckily, the NAPRA Model Standards vastly raises the criteria for hiring personnel, enforcing policies and procedures, ensuring clean facilities and proper equipment, and keeping a general maintenance log.[176] Adoption of the Model Standards should make provincial/territorial oversight easier and lower the risk of public health issues.

With regards to personnel involved with sterile preparations, including pharmacists, pharmacist technicians, and pharmacist assistants, each individual must attain the appropriate education, experience, and required trainings and assessments in order to participate in the process of compounding of sterile preparations.[177] The training and assessments include the following:

> [R]eading and understanding the policies and procedures related to compounded sterile preparations; theoretical training, with assessment covering various topics . . . ; individual practice training and assessment in the workplace clean room . . . ; assessment of aseptic techniques, based on gloved fingertip sampling (GFS) and media fill tests, for various types of sterile preparations to be compounded.[178]

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[175] *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), http://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_Hazardous_Sterile _Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), NAPRA, https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous _Sterile_Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), NAPRA, https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf.

[176] *Id.*

[177] *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.

[178] *Id.*

Trainings and assessments must be complete at least once a year in the work place for personnel operating at low or medium risk levels and at least twice a year for preparation with high risk levels.[179] Should any compounding personnel fail an assessment, the work shall be immediately halted and retraining will be required.[180] All assessments and trainings are recorded in each employee's file and must be retained for a period specific to the provincial/territorial authority.[181]

Pharmacies conducting sterile preparation require an on-site sterile compounding supervisor, separate from a pharmacy manager or department head.[182] The sterile compounding supervisor ensures that requirements by the Model Standards are met and all records are available for audit and inspection by provincial/territorial authorities.[183]

One of the main responsibilities for a sterile compounding supervisor is to establish the content for all policies and procedures.[184] Further, the content must provide a detailed description of all activities occurring in the pharmacy.[185] Procedures must be clear and concise, follow a standard format, and include an index for easy access.[186] Established policies and procedures must be promptly updated should there be a change in practice or standards.[187] Even without changes, policies and procedures must be reviewed every three years by the sterile compounding supervisor.[188] If the compounding of a drug is prepared by more than one pharmacy, as permitted by provincial/territorial legislation, the dispensing pharmacy should include information about the acquisition of compounded sterile preparations for patients in its policies and procedures.[189]

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179 *Id.*
180 *Id.*
181 *Id.*
182 *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.
183 *Id.*
184 *Id.*
185 *Id.*
186 *Id.*
187 *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.
188 *Id.*
189 *Id.*

Compliance with the policies and procedures prescribed by the sterile compounding supervisor ensures proper quality and safety of the prepared drugs.

The Model Standards for Compounding of Non-Sterile Preparations similarly follow suit as a means of increasing accountability within compounding facilities. Along with the specified training and assessment of personnel, specialized equipment, and policies and procedures for quality assurance, Non-Sterile Preparations specifically require that a risk assessment be completed prior to compounding to identify the appropriate level of requirements to minimize contamination of each compounded product and provide adequate protection for personnel.[190] There are three levels of requirements, Level A, B, and C, where compounded drugs are categorized by how the product is defined under the USP *General Chapter <795>*, the quantity of ingredients being compounded, and whether the product is hazardous.[191] Level A has the lowest requirement, requiring only a separate space designated for compounding. However, Level B and C have more stringent requirements. For example, one of the requirements under Level C is a well-ventilated room with appropriate air exchange and negative pressure.[192] Even though accountability may seem lower for certain non-sterile compounded drugs, such as simple and moderate compounds categorized as Level A, public threat is lessened for non-sterile compounded drugs based on the modality of consumer administration (i.e. oral vs. injectable).[193] Regardless, by conducting a risk assessment in compliance with the NAPRA Model Standards, consumers of non-sterile compounded drugs are better protected from incurring health problems.

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[190] *Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf.

[191] *Id.*

[192] *Id.*

[193] *Id.*; Edward Lamb, *What Is Nonsterile Drug Compounding?*, VERY WELL (Apr. 13, 2017), https://www.verywell.com/what-is-nonsterile-drug-compounding-2663873.

As a whole, the NAPRA Model Standards increase accountability within compounding pharmacies by requiring general maintenance logs.[194] These records include either computerized or paper documentation regarding activities such as cleaning and disinfecting, certification and maintenance of the facility, risk assessment, and certification of the primary engineering control and maintenance of other equipment.[195] Verification of proper operation of equipment and instruments (i.e. calibration, temperatures for different types of storage) must be documented.[196] All general maintenance logs must be retained according to the respective provincial/territorial authority, thus allowing provinces/territories to ensure that compounding facilities remain in compliance with these enhanced safety standards.[197]

Through the implementation of these three subsections of the NAPRA Model Standards for Compounding, the combination of oversight by provincial/territorial authorities and accountability by the pharmacies should be effective in ensuring safe compounding.

F. Canada's Possible Future Regulatory Disaster

While the NAPRA Model Standards for Pharmacy Compounding provide the framework for safe preparation, Canada now seems to be revisiting Dr. Thiessen's recommendations. Recently, Health Canada initiated a regulatory initiative to create a new framework for addressing commercial compounding.[198] Current "Policy on

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[194] *Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations,* NAPRA (Nov. 1, 2016), https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous _Sterile_Preparations_Nov2016_Revised_b.pdf; *Model Standards for Pharmacy Compounding of Non- Sterile Preparations,* NAPRA (Mar. 28, 2018), https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf; *Guidance Document For Pharmacy Compounding of Non-Sterile Preparations*; NAPRA (revised Jun. 2018), https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_
Preparations_Guidance_June2018_FINAL.pdf.

[195] *Id.*

[196] *Id.*

[197] *Id.*

[198] *Regulatory Initiative: Amendments to the Food and Drug Regulations – Commercial Compounding – Forward Regulatory Plan 2018-2020*, GOV. OF

Manufacturing and Compounding Drug Products in Canada" defines the difference between manufacturing and compounding in order to determine whether an activity is provincially/territorially or federally regulated.[199] However, without concise regulatory oversight, a gap remains, creating public health issues.[200]

For Health Canada, there are inherent reasons to justify a cautious approach to this new regulatory initiative. Prior to creating the Model Standards for Pharmacy Compounding, Canada closely followed the U.S. guidelines and policies for compounding drug products.[201] This is exemplified by Canada's "Policy on Manufacturing and Compounding Drug Products in Canada" that addresses the notion that pharmaceutical compounding is not a means of bypassing federal drug review and approval systems.[202] More specifically, compounded drug products must result in a customized medication that does not duplicate an existing federally approved drug.[203] Health Canada also utilizes the U.S. Pharmacopoeia guidelines for the preparation of sterile and non-sterile compounds.[204] While following U.S. guidelines has not been detrimental to Canada's regulatory framework thus far, should Health Canada continue to pursue the U.S.' currently enacted Compounding Quality Act, regulatory loopholes may arise.

CANADA (Oct. 12, 2018), https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/2016-2018/regulatory-initiative-amendments-food-drug-regulations-commercial-compounding.html.

199 *Policy on Manufacturing and Compounding Drug Products in Canada*, *supra* note 55.

200 *Regulatory Initiative: Amendments to the Food and Drug Regulations – Commercial Compounding – Forward Regulatory Plan 2018-2020*, GOV. OF CANADA (Oct. 12, 2018), https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/2016-2018/regulatory-initiative-amendments-food-drug-regulations-commercial-compounding.html.

201 Jennifer Guderman, et al., *Potential Risks of Pharmacy Compounding*, NCIB (Mar. 23, 2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627035/.

202 *Id.*

203 *Id.*

204 United States Pharmacopeia standards <795> and <795> establish guidelines for the preparation of sterile and non-sterile compounding, respectively. *Policy on Manufacturing and Compounding Drug Products in Canada*, *supra* note 55.

V. CURRENT AND FUTURE IMPLICATIONS ON PRICES AND AVAILABILITY OF DRUG COMPOUNDS

A. United States

While the production of safe compounded drugs remains a top priority for the FDA, the Drug Quality and Security Act has made it less financially feasible for traditional compounding pharmacies to be profitable in the market.[205] Operating with lower profits, several pharmaceutical compounding companies have been forced to reduce the number of drugs produced.[206] Leiter's Compounding Pharmacy, at one time producing an astonishing 1,800 drugs, was compelled to lower production to only 11 drugs due to new FDA restrictions.[207] In addition, compounding pharmaceutical companies have been obligated to employ fifteen to twenty quality assurance staff members to ensure compliance with the stricter regulations.[208] The combination of reducing the number of drugs produced,[209] hiring additional employees,[210] and producing compounded drugs in small quantities due to rigid prescription requirements,[211] has driven up the cost of production tremendously.[212]

Ultimately, consumers are the ones paying the price as many compounded drugs will be either unavailable or are priced out of the reach of those that need them.[213] According to Charles Leiter, owner of Leiter's Compounding Pharmacy, physicians are finding it difficult to obtain medications necessary to treat their patients.[214] In par-

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[205] *Stricter Drug Compounding Regulations Complicate Ophthalmology Care*, *supra* note 89.

[206] *Id.*

[207] *Id.*

[208] *Id.*

[209] *Id.*

[210] *Stricter Drug Compounding Regulations Complicate Ophthalmology Care*, *supra* note 89.

[211] *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry,* FDA (Dec. 2016), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.

[212] *Stricter Drug Compounding Regulations Complicate Ophthalmology Care*, *supra* note 89.

[213] *Id.*

[214] *Id.*

ticular, Avastin utilized by retina physicians has been nearly impossible to acquire.[215] Avastin, an FDA approved medication used as a chemotherapeutic treatment for colon cancer, has also been successfully used for diseases such as macular degeneration, retinal vascular disease, and diabetic retinopathy.[216] In creating proper doses for retinal usage, compounding pharmacies must divide a four milliliter marketed dose into sixty single-use doses with each dose costing patients sixty dollars.[217] However, due to FDA enforcement and the prescription requirement under section 503A, many compounding pharmacies have stopped offering Avastin making it practically unavailable.[218] Without the compounding pharmacies' offerings of Avastin, patients are left with two FDA approved drugs, Lucentis and Eylea, costing approximately $2,020 and $1,950 respectively.[219] In such cases, many patients, with or without insurance, simply cannot afford the exorbitantly expensive medications, while viable medications costing 97 percent less than their FDA approved counterparts are simply unavailable due to government overregulation.[220] Simply stated, in the government's efforts to protect consumers through strict regulation and requirements, smaller compounding companies are unable to comply due to the high costs of meeting those requirements and are penalized to the point that consumers lose their access to needed medications.[221]

On January 4, 2018, the FDA announced that the USP standards are currently under revision with the intent of raising the standards for drug compounding production.[222] All compounding pharmacies

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215 *Id.*

216 Robert Wong, *We Want Access to Safe and Effective Avastin. Here's a Solution.,* KEVINMD (Feb. 15, 2016), https://www.kevinmd.com/blog/2016/02/want-access-safe-effective-avastin-heres-solution.html.

217 *Id.*

218 *Id.*

219 *Id.*

220 *Id.*

221 Robert Wong, *We Want Access to Safe and Effective Avastin. Here's a Solution.,* KEVINMD (Feb. 15, 2016), https://www.kevinmd.com/blog/2016/02/want-access-safe-effective-avastin-heres-solution.html.

222 *FDA Aims to Strengthen Oversight of Compounded Drug Manufacturing,* BIOPHARM DIVE (Jan. 4, 2018), https://www.biopharmadive.com/news/fda-strengthen-oversight-compounded-drug-manufacturing-nejm/514097/.

under 503A will be required to implement the USP's revised standards.[223] Although there is no indication as to the manner in which the USP standards will be modified, it is reasonable to assume that pharmacists will need to be retrained and be reassessed to prove competency. Furthermore, compounding pharmacies may be required to purchase new or additional equipment to ensure the safe preparation of sterile drug compounds. While a safer product is potentially in our future, the additional requirements placed on compounders may cause an economic burden so great as to cause smaller compounding pharmacies to close shop.

Additionally, should Congress amend the Compounding Quality Act, mandating outsourcing facilities to register with the FDA, those outsourcing facilities may choose to close their doors as well. For exemption from the prescription requirement in section 503A, outsourcing facilities need to meet the following criteria:

1. The outsourcing facility is in compliance with CGMPs.[224]
2. A compounded drug can not contain bulk drug substances unless the substance appears on a list established by the secretary when there are clinical needs.[225]
3. Ingredients (other than bulk substances) used in compounds must comply with standards of the USP, NF, or of another compendium.[226]
4. The drug does not appear on a list published by the Secretary because it's unsafe or ineffective.[227]
5. The drug is not an "essential copy" of one or more approved drugs.[228]
6. The drug doesn't present demonstrable difficulties for compounding.[229]
7. The outsourcing facility has a proper control system when dealing with compounded drugs or ingredients that are subject to the FDA's risk evaluation and mitigation strategy.[230]

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[223] *Id.*

[224] *Drug Quality and Security Act,* Pub. L. No. 113-54, 127 Stat. 587 at §503B(a)(1) (2013).

[225] *Id.* at §503B(a)(2).

[226] *Id.* at §503B(a)(3).

[227] *Id.* at §503B(a)(4).

[228] *Id.* at §503B(a)(5).

[229] *Id.* at §503B(a)(6).

[230] *Id.* at §503B(a)(7).

8. The outsourcing facility that compounds the drug is the only entity that can sell the drug.[231]

9. The drug must be labeled appropriately.[232]

The difficulty in meeting these requirements is obvious as the FDA has issued warning letters to eight out of the seventy-three registered outsourcing facilities, stating that they are failing to meet the requirements under section 503B.[233] The FDA has also ordered two facilities to cease sterile operations and recall dispensed sterile products.[234] The combination of increased FDA scrutiny along with significant increases, approximately five to ten times, in costs to achieve the CGMP requirements,[235] has outsourcing facilities questioning whether the financial investment is worth making. As a result, with massive shortages of over 300 essential drugs, in which outsourcing facilities normally assist in meeting those needs,[236] conditions will continue to deteriorate and leave patients without medications to treat their ailments.

Should the U.S. maintain its narrow and single approach towards public health protections, patients will no longer have access to effective and affordable treatments. As such, federal and state laws and regulations need modification to not only ensure the safety of compounded drugs, but to ensure drug availability with reasonable consumer costs. Creating a system of uniform accountability between states, along with shifting some responsibility to the compounding companies in a similar fashion to NAPRA Model Standards, may be an effective way to accomplish this balance. The more stringent FDA restriction created through the Compounding Quality Act does not seem to achieve this necessary balance.

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231 *Id.* at §503B(a)(8).

232 *Id.* at §503B(a)(10).

233 *Registered Outsourcing Facilities*, *supra* note 139.

234 *Id.*

235 *Stricter Drug Compounding Regulations Complicate Ophthalmology Care, supra* note 89.

236 *U.S. Compounding Pharmacies Market: Segment Snapshot and Table of Content 2015-2021*, DIGITAL J. (Dec. 14, 2017), http://www.digitaljournal.com/pr/3596354.

B. Canada

The NAPRA's strict standards for facility design and equipment for sterile compounding have resulted in costly and time consuming renovation for many compounding facilities.[237] Regarding facility design, some of the requirements include the following:

1. A reserved area large enough for sterile preparations – ensure good flow of people, equipment and materials; and allow disinfecting and cleaning without constraint.[238]

2. Heating, ventilation, and air conditioning systems must be designed to minimize risk of airborne contamination in controlled rooms.[239] Specifically return air intakes must be placed at the bottom of the walls to push any possible contaminants downward.[240]

3. Controlled rooms must not have any windows or openings that lead to the outside or non-controlled rooms.[241] If they do, they must be sealed.[242]

4. A clean room, where atmospheric properties are controlled.[243]

5. An anteroom, which is the transition space between a non-controlled and controlled room.[244]

According to Sabrina McLean, a pharmacist and compounding consultant in Dartmouth, Nova Scotia, some pharmacies producing sterile compounds "would have to do *full* renovations to meet the requirements."[245] In achieving these lofty goals, some of these pharmacies have discontinued operations, while others have been forced to decrease production significantly.[246] Lawtons, a Nova Scotia

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[237] Alex Rose, Canada is Tightening its Drug Compounding Regulations, THE SIGNAL (Mar. 24, 2017), http://signalhfx.ca/canada-is-tightening-its-drug-compounding-regulations/.

[238] *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.

[239] *Id.*

[240] *Id.*

[241] *Id.*

[242] *Id.*

[243] *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.

[244] *Id.*

[245] Rose, *supra* note 237.

[246] *Id.*

pharmacy that participates in compounding, has dramatically decreased its compounding activity as an alternative to major facility renovations based on the new regulations.[247] Unfortunately, Canadian consumers, just like their peers in the U.S., may have no choice but to incur higher costs for their compounded drugs or simply do without as many pharmaceutical compounding companies are being overregulated out of the market.

Canada has not seen the full impact of the new regulations on drug prices and availability simply because the NAPRA has recently published the Model Standards for Non-Sterile Preparations.[248] It is McLean's assertion that the new regulations for non-sterile compounding will require the use of more expensive protective equipment.[249] While it is reasonable to speculate that the costs associated around non-sterile compounding will only be a small percentage compared to what it is for sterile compounding, costs may still be high enough to deter pharmacies from producing non-sterile compounds.

On the other hand, even with the NAPRA Model Standards largely increasing the overhead costs, some compounding pharmacies are not struggling with offsetting these high costs due to generous dispensing and compounding fee subsidized payments by provincial drugs programs.[250] In August 2017, Manitoba placed a $30 cap on compounding fee payments for non-sterile compounded drugs and a $60 cap for sterile compounded drugs per prescription.[251] Because pharmacies individually determine dispensing and compounding fees, clients became concerned that they would be required to pay additional fees above and beyond the payment caps.[252]

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247 *Id.*

248 *Model Standards for Pharmacy Compounding of Non-Sterile Preparations*, NAPRA (Mar. 28, 2018), https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_March2018_FINAL.pdf.

249 Rose, *supra* note 237.

250 Holly Caruk, *Pharmacy Fees Won't Be Passed on to Patients Says Pharmacists*, CBC NEWS (Aug. 22, 2017), http://www.cbc.ca/news/canada/manitoba/pharmacy-fees-won-t-be-passed-on-to-patients-say-pharmacists-1.4256244.

251 *Id.*

252 *Id.*

This was especially true for compounded drugs that could cost hundreds of dollars to produce.[253] Quinton Didyk, an owner of a compounding pharmacy that serves over half of the pharmacies in Manitoba, asserts that his customers will not be charged additional compounding fees due to the generous payment caps.[254] Additionally, the policy contains an exemption clause which states that specialty compounds or compounds that take more than forty-five minutes to prepare will be subsidized by provincial drug programs.[255] These regulated compounding fee payments allow compounding pharmacies to remain competitive and profitable while keeping prices affordable.

These fee payments are not quite as generous in other provinces.[256] Most provinces have dispensing fee payment caps around $8-12.[257] For example, Ontario has a cap starting at $8.83 and goes up to $13.25 depending on the location.[258] With such low payment caps, compounding facilities in other provinces are forced to choose whether to remain competitive, but less profitable, or gamble by charging higher fees which would require consumers to reach in their pockets. In the end, the latter choice may likely lead to a less profitable outcome as consumers may seek other sources of remediation. Should provinces decide to increase or match the payment caps set in Manitoba, compounding pharmacies would find it more financially feasible to remain and comply with the NAPRA Model Standards, thereby keeping compounded drugs available and affordable to consumers throughout Canada.

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253 *Id.*

254 *Id.*

255 Holly Caruk, *Pharmacy Fees Won't Be Passed on to Patients Says Pharmacists*, CBC NEWS (Aug. 22, 2017), http://www.cbc.ca/news/canada/manitoba/pharmacy-fees-won-t-be-passed-on-to-patients-say-pharmacists-1.4256244.

256 *Changes in Dispensing Fees*, GOV'T OF MANITOBA (July 2017), https://www.gov.mb.ca/health/pharmacare/dispensing_fees.html.

257 *Id.*

258 *Id.*

VI. CONCLUSION

With an ever-increasing population, drug shortages, and a growing need for customized medications, drug compounding will continue to be an essential component in the world of pharmaceuticals. While these drugs are desperately needed to fill the void in the market, the business of pharmaceutical compounding remains dangerous and, for the most part, unregulated in the U.S. despite Congress' passing of the Drug Quality and Safety Act, which defines state and federal authority and responsibilities in order to ensure consumer safety.[259] This has left many gaps in the regulatory framework, allowing sterile compounding pharmacies to function unchecked and unaccountable.[260] Incommensurable standards of quality and requirements for training between states, in conjunction with misaligned state and federal laws and regulations, continues to be the greatest impediment in the delivery of safe and high quality pharmaceuticals.[261] Moreover, Congress tied the FDA's hands when it opted against mandating outsourcing facilities from having to register with the FDA.[262] The FDA cannot effectively regulate outsourcing facilities when states undermine the incentives the FDA provides to voluntarily register.[263] At the same time, states that enforce regulations set by the Drug Quality and Safety Act have made it less financially viable for traditional compounding pharmacies due to strict scrutiny over sterile compounding practices and procedures.[264] Some pharmacies have chosen to drastically reduce the number of compounded drugs produced, while others have simply ceased operations.[265] Ultimately, consumers of drug compounds have less availability, are faced with higher prices, and remain vulnerable to potentially unsafe medications.

Similarly, Canadian pharmaceutical compounding continues to play a crucial role in the healthcare system. While it remains to be

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259 Drug Quality and Security Act, Pub. L. No. 113-54 (2013).

260 Silverman, *supra* note 14.

261 *Best Practices for State Oversight of Drug Compounding*, *supra* note 130.

262 *See id.*

263 Silverman, *supra* note 14.

264 *Stricter Drug Compounding Regulations Complicate Ophthalmology Care*, *supra* note 83.

265 *Id.*

seen whether the NAPRA Model Standards will be effective in ensuring consumer safety, the NAPRA has clearly placed the responsibility into the hands of pharmacy professionals.[266] Unlike the Compounding Quality Act in the U.S., the Model Standards provide compounding pharmacies with detailed guidelines in the preparation of compounds.[267] These clear and concise guidelines allow provincial/territorial authorities to easily enforce and maintain these high standards.[268] On the negative side, however, while the enforcement of such rigid NAPRA Model Standards maintains high compounding quality standards, costs are driven up by the requirements for upgraded facility design, sophisticated equipment, and better trained personnel.[269] Dramatically higher production costs have already driven several Canadian compounding pharmacies out of the market.[270] However, provinces may be able to find ways to incentivize pharmacies, thereby offsetting the costly changes required by the Model Standards.[271] Raising compounding fee payment caps would be an effective method of achieving this goal. With a bit of tweaking and creativity, Canada's regulatory initiatives appear to hold the most promise for procuring safe drug compounds without the risk of diminished availability or exorbitant prices.

The U.S. and Canada face a future which will require additional governmental action to secure the successful delivery of quality compounded medications. As noted by Michael Carome, MD, director of the Public Citizen Health Research Group in Washington, DC, "[a]lthough compounded drugs serve an important need for patients whose medical needs cannot be met by an FDA-approved drug, it is imperative that healthcare providers and patients alike recognize that compounded drugs pose a higher risk to patients than FDA-approved products."[272] Whether additional federal legislation is needed to bring compounded drugs up to FDA-approved stand-

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266 *Model Standards of Pharmacy Compounding for Non-Hazardous Sterile Preparation*, *supra* note 73.

267 *Id.*

268 *See generally id.*

269 Rose, *supra* note 237.

270 *Id.*

271 Caruk, *supra* note 250.

272 Kelly, *supra* note 149.

ards is a relevant question. In either case, a close working relationship between federal and state/provincial levels must exist for compounding to successfully and safely coexist with traditional pharmaceutical manufacturers. While both countries have made headway into developing effective strategies to accomplish these goals, collaboration, creativity, and a broad-minded willingness of state or provincial/territorial and federal governments to work together for the good of public health will be key to making compounding pharmacies profitable, safe, and able to meet the future demands of an ever-growing population.