Compounded Drugs

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Summary

Compounding has been traditionally defined as a process where a pharmacist or a physician combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Traditionally compounded drugs (CDs) are made in response to an individual prescription from a licensed health provider in the context of a pharmacist's and health care professional's relationship with a specific patient.

Some have suggested that certain activities not traditionally associated with compounding be considered compounding. Such activities include the large-scale production of drugs to ease certain drug shortages, to meet outsourcing needs of hospitals, and to supply physician-administered drugs. Non-traditional compounding may include (1) the production and shipping of large volume of drugs across state lines; (2) production of drugs that are copies of FDA-approved commercially available drugs; (3) provision of CD without a prescription for an individual patient to receive a compounded version and outside of a professional relationship; and (4) production of products to third parties, such as hospitals, clinics, physician offices, and home health providers. These activities could be considered more akin to manufacturing than traditional compounding, which is considered part of the traditional practice of pharmacy.

Adverse events involving contaminated compounded drugs have drawn attention to the growing use of non-traditionally compounded drugs in health care delivery. Shortages of sterile generic drugs and hospital outsourcing are cited as causes of increased numbers of CDs produced by non-traditional compounders. Efforts to assess the risks and benefits of CDs on public health and safety are complicated by the lack of publicly available information, including the absence of a federal adverse event reporting requirement, and the lack of information about the number of drugs compounded, the types of drugs compounded, and the number of businesses in this market.

Policymakers have raised questions regarding how best to improve the safety of CDs while maintaining patient access to needed medications. Drug compounding has historically been the focus of state governments through their regulation of pharmacies. Recently questions have arisen regarding the extent to which the federal government can regulate the practice of compounding through the Federal Food, Drug, and Cosmetic Act (FFDCA). Policy discussions include proposals to clarify federal oversight of high-risk activities and products, to improve federal and state coordination, and to increase use of existing federal authorities.

This report provides background information on CDs and non-traditional compounding pharmacies relevant to policy discussions. This includes an overview of the 2012 fungal meningitis outbreak, recent safety alerts and recalls of compounded drugs, definitions of traditional compounding and non-traditional compounding, information on the CDs produced and by whom, information on the demand for non-traditional compounding, including the role of shortages of sterile injectable drugs, hospital out-sourcing, and patient and provider demand, and information on adverse events involving compounded drugs.

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Introduction

In September 2012, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Tennessee Department of Health, and other state health departments[1] began investigating a rare, non-contagious outbreak of fungal meningitis.[2] As of June 3, 2013, 20 states had reported 745 infections (including fungal meningitis and other conditions),[3] and 58 deaths were traced to injections of contaminated, preservative-free methylprednisone acetate produced by the New England Compounding Center (NECC). NECC, which self-identified as a compounding pharmacy – not a manufacturer – and was licensed by the state of Massachusetts, produced large volumes of drugs that were shipped across state lines to health care providers.[4] Unlike traditional pharmacy practices, NECC produced drugs without individual prescriptions and made copies of existing commercially-manufactured drugs.[5]

These serious adverse events[6] drew attention to compounded drugs (CDs).[7] Six congressional hearings were held in 2012-2013 to understand the factors that led to these adverse events and ways to prevent future such incidents; these hearings are listed in **Appendix B**.[8] In these hearings Members of Congress and stakeholders raised questions regarding how best to improve the safety of CDs while maintaining patient access to needed drugs.

Issues raised at these hearings include the following: (1) what are CDs; (2) how are CDs made and by whom; (3) what is the role of CDs in health care delivery; (4) what are the federal and state roles in oversight of CDs; (5) how safe are CDs, and (6) what steps could be taken to prevent adverse events from CDs.

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[1] For more information on the events relating to tracking the fungal meningitis outbreak, see Beth Bell, Director, Director, National Center for Emerging and Zoonotic Diseases, Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS), "Testimony Before the Health, Education, Labor, and Pensions Committee, U.S. Senate: The CDC and Public Health Response to the 2012 Fungal Meningitis and Other Infections Outbreak," pp. 2-6, http://www.help.senate.gov/imo/media/doc/Bell.pdf.

[2] This form of fungal meningitis is non-contagious; the more common form of meningitis is bacterial and is infectious. See http://www.cdc.gov/meningitis/fungal.html.

[3] Centers for Disease Control and Prevention (CDC), *Multistate Fungal Meningitis Outbreak Investigation—Current Case Count*, accessed June 3, 2012, http://www.cdc.gov/hai/outbreaks/meningitis.html. This case count is updated monthly on the CDC website.

[4] Centers for Disease Control and Prevention, *Multistate Fungal Meningitis Outbreak Investigation*, accessed May 6, 2012, http://www.cdc.gov/HAI/outbreaks/currentsituation/; see also, http://www.cdc.gov/hai/outbreaks/meningitis-map.html.

[5] Statement of Margaret Hamburg before the Senate Committee on Health, Education, Labor, and Pensions "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," November 15, 2012, http://www.fda.gov/NewsEvents/Testimony/ucm327667.htm; A. Goodnough, "Sterility Found Lacking at Drug Site in Outbreak," *New York Times*, October 23, 2012, http://www.nytimes.com/2012/10/24/health/sterility-found-lacking-at-drug-site-in-meningitis-outbreak.html?ref=health.

[6] The Food and Drug Administration (FDA) defines a serious adverse event as any undesirable experience associated with the use of a medical product in a patient. For more information, see FDA "What is a Serious Adverse Event?" http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm.

[7] See FDA, "Pharmacy Compounding" http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

[8] In 2003 another hearing was held: "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding," hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003.

This report provides background information about these issues that may be used to inform the policy discussion as Congress considers legislation. This report focuses on (1) available background information on CDs and compounding pharmacies; (2) changes in the role of CDs in healthcare delivery; (3) factors leading to an increase of compounding; (4) safety of CDs, including a table of selected publicly available adverse events; and (5) a brief summary of policy issues raised to date. This report includes material on CDs for human patients and does not include a discussion of veterinary drug compounding or the compounding of dietary supplements.

Issues of public health and safety of CDs are tied to the regulation and oversight of CDs. This report includes brief information on federal, state, and professional efforts to increase the safety of CDs. Information on the federal regulation of CDs is addressed in other CRS reports: CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman, and CRS Report R43038, *Federal Authority to Regulate the Compounding of Human Drugs*, by (name redacted). Information on the regulation of commercially manufactured drugs can be found in CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by (name redacted).

Background

Compounding has been traditionally defined as a process where a pharmacist or a physician combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Traditionally CDs are made in response to an individual prescription from a licensed health provider in the context of a pharmacist's and health care provider's professional relationship with a specific patient. CDs provide alternatives to standard commercially-manufactured drugs when such drugs do not meet the unique medical needs of a patient (e.g., due to a need for an allergen-free drug, weight-based dosing, or alternate modes of delivery), or are unavailable due to discontinuation, unavailability, or shortages. Shortages of sterile generic drugs and hospital outsourcing are cited as causes of increased the reliance of health care providers on CDs.[9]

Some have suggested that certain activities not traditionally associated with compounding be considered compounding. Such activities include the large-scale production of drugs to ease certain drug shortages, to meet outsourcing needs of hospitals, and to supply physician-administered drugs. Non-traditional compounding may include (1) the production and shipping of large volume of drugs across state lines; (2) production of drugs that are copies of FDA-approved commercially available drugs; (3) production of drugs outside of a personal relationship with a patient and without a prescription for an individual patient to receive a compounded version; and (4) providing products to third parties, such as hospitals, clinics, physician offices, and home health providers. These activities may be considered more akin to manufacturing than traditional compounding, which is considered part of the traditional practice of pharmacy. In this report, references to these types of activities will be called "non-traditional compounding." This report will be updated as necessary.

[9] Office of the Inspector General, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them*, Department of Health and Human Services, OEI-01-13-00150, Washington, DC, April 1, 2013; K. Fiore, "Drug Shortages Spark Use of Compounders," (October 18, 2012), http://www.medpagetoday.com/MeetingCoverage/ASA/35406.

Health Concerns Involving CDs

Background

Adverse events stemming from CDs in 2012 are the starting point for the current policy debate about existing regulatory oversight of CDs.[10] The 2012 fungal meningitis outbreak was triggered by contaminated sterile CDs, injectable methylprednisolone, and was the worst recorded adverse event involving CDs,[11] with news reports indicating that up to 14,000 individuals were exposed to this product.[12] Contaminated sterile drugs pose the most serious threats to human health, and can cause death.[13] Details on this event are listed in the following text box.[14]

Fall 2012 Fungal Meningitis Events

- September 26, 2012, NECC recalls three lots of methylprednisolone acetate, an injectable steroid.
- October 4, 2012, the FDA verified that NECC, a compounding center in Massachusetts, was the source of the contaminated compounded injectable methylprednisolone.[15]
- October 6, 2012, NECC recalled all compounded products from its Framingham, MA facility.[16] The FDA urges health care providers to follow up with patients who received injectable and ophthalmic products.
- October 31, 2012, Ameridose, a company associated with NECC, recalled all unexpired products in circulation.

Source: CDC "Related Drug Recalls" http://www.cdc.gov/hai/outbreaks/currentsituation/archive.html, accessed May 6, 2012.

The safety of CDs has been a concern of Congress for over two decades due to the expansion of non-traditional compounding.[17] Potential safety risks for CDs include problems with *potency* (i.e.,

[10] An adverse event involving the same type of contaminated compounded drug and fungal infection was reported as recently as May 24, 2013, see FDA, "Main Street Family Pharmacy in Tennessee: FDA Alerts Health Care Providers of Adverse Reactions Associated with Steroid Injections," http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm353953.htm.

[11] M.R. Cohen, "Meningitis cases spotlight broken system," Philly.com, October 17, 2012, http://www.philly.com/philly/health/Meningitis-cases-spotlight-broken-system.html.

[12] J. Aleccia, "Fungal Meningitis Outbreak Tied to Steroid Shots, Isn't the First, Reports Show," October 18, 2012, http://vitals.nbcnews.com/_news/2012/10/18/14517177-fungal-meningitis-outbreak-tied-to-steroid-shots-isnt-the-first-reports-show?lite.

[13] Ibid., p. 5.

[14] An expanded overview of events related to the 2012 fungal meningitis outbreak can be found in CRS Report R42837, *Selected Resources on Federal Oversight of Compounding Pharmacies*, by (name redacted), (name redacted), and (name redacted).

[15] Beth Bell, Director, National Center for Emerging and Zoonotic Diseases, Centers for Disease Control and Prevention, HHS, "Testimony Before the Health, Education, Labor, and Pensions Committee, U.S. Senate: The CDC and Public Health Response to the 2012 Fungal Meningitis and Other Infections Outbreak," p. 6, http://www.help.senate.gov/imo/media/doc/Bell.pdf.

[16] See CDC "Related Drug Recalls" http://www.cdc.gov/hai/outbreaks/currentsituation/archive.html, accessed May 6, 2012.

[17] For information on Congressional concerns regarding drug compounding that led to Section 503A, see U.S. Congress, Senate Committee on Labor and Human Resources, *Food and Drug Modernization and Accountability Act of 1997*, S. 830, 105th Cong., 1st sess., July 1, 1997, S.Rept. 105-43, pp. 67-69. For information on recent concerns with some references to the history of federal oversight, see "Pharmaceutical Compounding: Proposed Legislative Solution," hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, May 9, 2013; "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, (continued...)

the dosage is inaccurate, either too strong or too weak), *purity* (e.g., the drug contains other chemicals that could be harmful), and *contamination* (the drug is contaminated with a bacteria, fungus, or virus).[18]

The FDA conducted surveys in 2001 and 2006 to assess identity, strength, quality and purity issues for CDs. [19] In a non-random survey of compounded drugs available over the Internet, about one-third (33%) failed analytic testing, mostly regarding potency or uniformity of dosage. In these surveys, the rates of analytic testing failures for compounded drugs were higher than those for commercially-available drugs, where only 2% of drugs failed analytic testing.[20] There is no specific federal or state requirement that an individual CD be tested for potency, purity, and sterility prior to being sold or administered.[21] The compounder of a product may voluntarily perform such tests along with other quality control processes.[22]

Safety issues with CDs also have been found by state pharmacy boards. [23] Certain states have started testing a certain percentage of compounded drugs for non-disciplinary purposes. For example, the State of Missouri Board of Pharmacy initiated a testing program in 2003 for compounded drugs and each year tests a certain number of finished products.[24] Over the course of the testing program, 15% - 25% of the CDs were found to have problems with drug potency, ranging from a sub-potent drug with 0%—no active ingredient present—to a super-potent drug with almost 400% of the prescribed dosage. An inaccurate dose may present a risk of harm to the patient through a risk of toxicity (super-potent) or the risk of ineffective treatment (sub-potency) (see for example, **Table C-1**, years 2010, 2007). [25]

(...continued)

April 26, 2013; "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 15, 2012; "The Fungal Meningitis Outbreak: Could It Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 14, 2012 "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding."

[18] See US Pharmacopeial Convention-NF, General Chapter <797> Pharmaceutical Compounding – Sterile Preparations and USP-NF <795> Non-Sterile Compounding.

[19] See FDA, "Results" of "Report: Limited FDA Survey of Compounded Drug Products," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm; "Stabilityhttp://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm.

[20] Ibid., and FDA, "Results of Report: Limited FDA Survey of Compounded Drug Products," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm.

[21] See National Council of State Legislators, "State Regulation of Compounding Pharmacies," http://www.ncsl.org/issues-research/health/regulating-compounding-pharmacies.aspx; Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

[22] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington, DC, p.3.

[23] A report from Rep. Markey's office details safety issues brought to state boards and transmitted to that office, see http://markey.house.gov/sites/markey.house.gov/files/documents/Compounding%20Pharmacies%20-%20Compounding%20Risk%20FINAL_0.pdf.

[24] See Missouri Board of Pharmacy annual reports 2006-2011, http://pr.mo.gov/pharmacists-annual-reports.asp.

[25] T. Mullarkey, "Pharmacy Compounding of High-Risk Products and Patient Safety," *American Journal of Health-System Pharmacists*, vol. 66 (Suppl5), (September 1, 2009), p. S9.

The lack of resources to carry out testing of CDs appears to be a problem in several states.[26] For example, a newspaper reported that Texas passed a law to provide for inspections of compounding pharmacies, but did not authorize funds for such purposes until 2007; once funded, testing dropped by two-thirds in 2012 compared to 2010 due to state budget cuts.[27]

Adverse Event Reporting

There is no federal requirement for producers of CDs to report adverse events, so the actual number of individuals harmed by CDs is unknown.[28] Policymakers have had concerns with CDs[29] that date back almost two decades;[30] these include reports of contamination of products that should be sterile, sub- or super-potent dosages, and impurities.[31]

Table C-1 provides a selected compilation of publicly available reports of adverse events involving CDs and other compounded medical products with details about the date, the number of states affected, the number of people affected, mortality (if any), drug involved, condition treated, and other characteristics, such as whether the product was shipped across state lines or was an off-label use.[32] The vast majority of these adverse events involve sterile compounded products.[33] Sterile compounded products include injectable drugs, IV-delivered drugs and solutions,

[26] See discussion of limited state resources in the public meeting: "Framework for Pharmacy Compounding: State and Federal Roles," December 19, 2012, starting on p. 22, http://www.fda.gov/downloads/NewsEvents/MeetingsConferencesWorkshops/UCM335791.pdf.

[27] E. Dexheimer, "As Pharmacies Face Scrutiny, State Oversight Drops," *Austin Statesman*, November 3, 2012, accessed May 20, 2013. See also, National Association of Boards of Pharmacy, "Texas Board Surveys Pharmacies About Compounding Practices, Will Seek Legislative Support for Additional Inspectors," http://www.nabp.net/news/texas-board-surveys-pharmacies-about-compounding-practices-will-seek-legislative-support-for-additional-inspectors, accessed May 20, 2013.

[28] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

[29] U.S. General Accounting Office, *Prescription Drugs: State and Federal Oversight of Drug Compounding by Pharmacies*, 04-195T, September 23, 2003, http://www.gao.gov/products/GAO-04-195T.

[30] Information on these concerns can be found on FDA webpages of adverse events, warning letters, manufacturer recall notices, and in professional journals. See section: "Articles from Legal, Professional, and Scientific Journals" in CRS Report R42837, *Selected Resources on Federal Oversight of Compounding Pharmacies*, by (name redacted), (name redacted), and (name redacted); and FDA, "Results" of "Report: Limited FDA Survey of Compounded Drug Products," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm.

[31] For a selected group of resources see CRS Report R42837, *Selected Resources on Federal Oversight of Compounding Pharmacies*, by (name redacted), (name redacted), and (name redacted); also, FDA "Pharmacy Compounding," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm; and FDA, "Introduction: 2006 Limited FDA Survey of Compounded Drug Products," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm.

[32] Off-label use of a prescription drug or device refers to the ability of licensed health care providers to prescribe or use the drug for indications, conditions, patients, dosages or routes of administration not yet evaluated and approved by the FDA as part of a new drug approval application.

[33] Sterile compounding differs from non-sterile compounding. When compounding exclusively with sterile ingredients, sterility must be maintained in all phases of production; when compounding with non-sterile ingredients, sterility must be achieved for the finished product. These processes require special equipment, facilities, and personnel training. See T. Mullarkey, "Pharmacy Compounding of High-Risk Products and Patient Safety," *American Journal of Health-System Pharmacists*, vol. 66 (Suppl5), (September 1, 2009), p. s5; see USP-NF, "General Chapter <797> Pharmaceutical Compounding – Sterile Preparations," http://www.usp.org/store/products-services/usp-compounding.

inhalation drugs, and parenteral nutrition that are administered directly into the body and must be sterile to assure patient safety.[34]

There is no specific federal requirement for the reporting of adverse events with CDs; so that this information is by nature selective and cannot be used to draw inferences about the overall risks of CDs. Reports of incidents with CDs that do not rise to adverse events are excluded from the table.[35] **Table C-1** also includes other characteristics of CDs, including where it was evident that CDs were shipped across state lines, an element of non-traditional compounding and high-volume facilities, whether CD were prescribed for off-label uses, and whether a drug shortage was in effect. For example, a shortage of generic preservative-free methylprednisolone was reported by some sources prior to the 2012 fungal meningitis outbreak, which was caused by compounded versions of that drug.[36]

The 2012 fungal meningitis outbreak led to greater scrutiny by federal and state authorities of sterile CDs.[37] In 2013, FDA and state authorities inspected certain facilities that produce sterile CDs and found a variety of safety concerns.[38] Later, some, but not all, of these compounders issued product recalls due to sterility concerns.[39] The next adverse event linked to a non-traditional compounding pharmacy occurred on May 24, 2013, when the FDA reported infections linked to contaminated sterile injectables; on May 28, 2013, the compounder recalled certain sterile products.[40] Recalls of sterile CDs for 2013 are listed in the following text box.[41]

[34] E. S. Kastango, American Society of Health-System Pharmacists, "The ASHP Discussion Guide for Compounding Sterile Preparations," http://www.ashp.org/s_ashp/docs/files/HACC_797guide.pdf.

[35] Some reports included concerns with products, but no adverse events. See for instance, M.P. Goldman, "Sodium Tetradecyl Sulfate for Sclerotherapy Treatment of Veins: Is Compounded Pharmacy Solution Safe?" *American Society for Dermatologic Surgery,* vol. 30, pp. 1454-1456; K. Hundley, "Lincare Pharmacy Runs Afoul of Missouri Regulators," St. Petersburg Times, April 18, 2003; S. Sellars and W.H. Utian, "Pharmacy Compounding Primer for Physicians: Prescriber Beware, " *Drugs*, vol. 72, no. 16, pp. 2043-2050.

[36] In early 2012, Hospira was listed on the FDA shortages website as discontinuing methylprednisolone: http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050794.htm. Another site reports a shortage of methylprednisolone in May 2012, http://eraycollins.blogspot.com/2012/05/shortage-of-injectable.html; and K. Kindy, L.H. Sun, and A. Crites, "Compounding pharmacies have been linked to deaths, illnesses, and safety failures for years," *Washington Post*, February 7, 2013, http://articles.washingtonpost.com/2013-02-07/national/36970682_1_medications-for-individual-patients-massachusetts-pharmacy-meningitis-outbreak.

[37] See Testimony of Margaret Hamburg at a hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented?", April 26, 2013.

[38] FDA, 2013 Inspections, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm, accessed May 6, 2012 and http://www.fda.gov/Safety/Recalls/default.htm, accessed May 6, 2012.

[39] Ibid.

[40] See FDA, http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm353953.htm.

[41] This list of recalled CD is current as of May 31, 2013. Additional notices can be found at http://www.fda.gov/Safety/MedWatch/default.htm.

2013 Manufacturer Recalls of Sterile CDs

As of May 31, 2013

- On May 29, 2013, Lowlite Investments (doing business as Olympia Pharmacy) announced a voluntary multi-state recall of all sterile drug products supplied to patients and offices of licensed medical professionals with a use by date of September 25, 2013, or earlier. The recall is being initiated due to concerns associated with prior quality control procedures that impacted sterility assurance. No adverse events had been reported as of the date of the recall.[42]
- On May 24, 2013, the FDA posted a notice that the CDC, the Tennessee Board of Pharmacy and the FDA were investigating reports of seven adverse events associated with compounded preservative-free methylprednisolone injections compounded by Main Street Family Pharmacy, LLC. These reports link infections, one of which is fungal in nature.[43] On May 28, 2013, Main Street Family Pharmacy, LLC recalled all sterile products with a use by date on or before November 20, 2013.[44]
- On May 15, 2013, the FDA announced that Pentec Health, Inc. initiated a recall of nutritional prescriptions for renal patient due to a lack of sterility assurance. No adverse events had been reported as of the date of recall.[45]
- On May 6, 2013, the FDA alerted health care providers of concerns regarding sterility assurance for sterile drugs produced and distributed by the Compounding Shop. The FDA reports that the Compounding Shop is in the process of recalling products. No adverse events had been reported as of the date of recall.[46]
- On April 22, 2013, Nora Apothecary and Alternative Medicine recalled all lots of sterile compounded products produced on or before April 19, 2013 due to the lack of sterility assurance and concerns associated with the quality control processes. No adverse events had been reported as of the date of recall.[47]
- On April 17, 2013, Balanced Solutions Compounding Pharmacy (Balanced Solutions), a division of Axium Healthcare Pharmacy, Inc., of Lake Mary, FL, recalled all lots of its sterile non-expired drug products due to a lack of sterility assurances associated with the quality control processes. No adverse incidents had been reported as of the date of recall.[48]
- On April 15, 2013, NuVision Pharmacy recalled all lots of all compounded lyophilized products due to sterility assurance concerns. No adverse events had been reported as of the date of recall.[49] On May 18, 2013, the FDA expanded its alert to health care providers to all sterile drug products made and distributed by NuVision.[50]
- On April 15, 2013, ApothéCure, Inc. recalled all lots of all sterile products compounded, repackaged, and distributed by Apothécure, Inc. due to sterility assurance concerns. No adverse events had been reported as of the date of recall.[51]
- On April 05, 2013, Green Valley Drugs recalled all lots of all sterile products compounded, repackaged, and distributed by the firm due to quality control concerns. No adverse events had been reported as of the date of recall.[52]

[42] See FDA, http://www.fda.gov/Safety/Recalls/ucm354450.htm.

[43] See FDA, http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm353953.htm.

[44] See FDA, http://www.fda.gov/Safety/Recalls/ucm354182.htm?source=govdelivery.

[45] See FDA http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm352939.htm.

[46] See FDA http://www.fda.gov/Safety/Recalls/ucm351841.htm.

[47] See http://www.fda.gov/Safety/Recalls/ucm349040.htm.

[48] See http://www.fda.gov/Safety/Recalls/ucm348723.htm.

[49] See FDA Recalls: http://www.fda.gov/Safety/Recalls/ucm348095.htm.

[50] See FDA http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm352949.htm?source=govdelivery.

[51] See FDA Recalls: http://www.fda.gov/Safety/Recalls/ucm348094.htm.

[52] See FDA Recalls: http://www.fda.gov/Safety/Recalls/ucm347559.htm.

- On March 25, 2013, state regulators halted production of sterile products made by Pallimed, a compounding pharmacy, and requested a recall of all sterile products.[53] Pallimed issued such a recall March 26, 2013. No adverse events had been reported as of the date of recall.[54]
- On March 20, 2013, Clinical Specialties Compounding Pharmacy recalled all sterile products repackaged and distributed due to the company's lack of confidence in product sterility.[55] This followed a recall on March 18, 2013, of Avastin compounded for ophthalmic use. No adverse events had been reported as of the date of recall.[56]
- On March 17, 2013, Med Prep recalled all lots of its compounded drugs due to mold contamination.[57] This followed the recall of a single product line on March 16, 2013. No adverse events had been reported as of the date of recall.[58]

Traditional Compounding

Traditional compounding is a process where a pharmacist or a physician "combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient"[59] in response to a prescription from a health care provider. CDs can include different formulations of drugs (e.g., liquid instead of tablet), doses, and certain ingredients (e.g., allergen-free, dye-free).[60] This report will use the phrase "traditional compounding" to reference the historical use of the term compounding.

CDs can provide patients drugs tailored to their individual health needs. The benefits of traditional compounding include (1) providing individualized drugs when commercially-produced drugs do not meet the health requirements of an individual patient; and (2) maintaining access to certain prescription drugs that are not commercially available due to shortages, unavailability, or discontinuation, among other factors.[61]

The number of CDs made cannot be determined due to the lack of publicly available information.[62] Currently no federal reporting requirement exists for producers of CDs with respect to their compounding activities.[63] The most recent attempt to assess the number of CDs

[53] C. Conaboy and K. Lazar, "State Halts Drug Production at Woburn Pharmacy," *Boston Globe*, March 24, 2013, http://bostonglobe.com/lifestyle/health-wellness/2013/03/25/woburn-compounding-pharmacy-issues-recall-sterile-products/j7QDTvv5WIHO1FU8W6mNGP/story.html.

[54] See FDA http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/.

[55] See FDA "Recall – Firm Press Release", http://www.fda.gov/Safety/Recalls/ucm344786.htm?source=govdelivery.

[56] See FDA Recalls http://www.fda.gov/Safety/Recalls/ucm344377.htm.

[57] FDA, "Medprep Consulting Inc. Announces Voluntary Nationwide Recall of all Lots of all Compounded Products Due to Potential Mold Contamination," March 17, 2013, http://www.fda.gov/Safety/Recalls/ucm344787.htm.

[58] See FDA Recall: http://www.fda.gov/Safety/Recalls/ucm344189.htm.

[59] "Thompson v. Western States," 535 U.S. 357 at 360-361.

[60] Ibid.

[61] Ibid., p. 361. Cost may be a factor in certain circumstances, see D. J. DeNoon, reviewed by L.J. Martin, "FDA: Pharmacies Can Still Make Preterm Birth Drug," http://www.webmd.com/baby/news/20110330/fda-generic-makena-ok; and "FDA Statement on Makena" http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279098.htm.

[62] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

[63] Comments of Margaret Hamburg, Commissioner of Food and Drugs, FDA, transcript of public meeting "Framework for Pharmacy Compounding: State and Federal Roles," December 19, 2012.

was through a survey commissioned by the FDA in 2001. This report estimated that 650 pharmacies filled about 13 million prescriptions for compounded prescription drugs per year.[64] Some stakeholders estimate that anywhere from 1-5% of all prescriptions filled annually are for CDs,[65] but the basis of this information cannot be verified. [66]

There is also no publicly available information on the types of CDs made, for instance, the percentage of CDs that include dosage, formulation, or ingredient alterations, or that are produced in response to shortages of commercially-manufactured drugs. The lack of information on the current scope of compounding presents challenges for public health authorities and policy makers.

Pharmacists, or technicians supervised by a licensed pharmacist, and physicians can produce CDs.[67] Compounding is part of the standard practice of pharmacy and is within the scope of state licensure of pharmacists and pharmacies.[68] The number of pharmacists engaged in compounding on a regular basis is difficult to evaluate due to a lack of publicly available information.[69] The most recent attempt to survey pharmacists, commissioned by the FDA, found that the majority of compounded prescriptions are filled by a small number of pharmacies, and for some, CDs are the majority of their business.[70] Others provide different estimates. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER), stated in a recent interview that 28,000 pharmacies compound drugs nationwide. [71] The American Pharmacists Association (APhA), a trade association of pharmacists, reports that there are 7,500 pharmacies in the United States that specialize in compounding.[72] The International Academy of Compounding Pharmacies, a trade

[64] Testimony of Steven Galson, FDA, at a hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003, "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding."

[65] Since close to 4 billion prescriptions are filled annually in the United States, this percentage would yield a range of 40 million-200 million CDs annually.

[66] P. M. Barrett, "America's Shadow Pharmacies," *Bloomberg Businessweek*, November 14, 2012; and Denise Grady, Sabrina Tavernise, and Andrew Pollack, "In a Drug Linked to a Deadly Meningitis Outbreak, a Question of Oversight," *New York Times*, October 4, 2012, http://www.nytimes.com/2012/10/05/health/news-analysis-a-question-of-oversight-on-compounding-pharmacies.html. Another estimate of 30 million-50 million annually is from the FDA, see Testimony of Steven Galson, FDA, at a hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003, "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding."

[67] States license health care professionals. The scope of permitted activities of pharmacy professionals is largely determined by state law. For an example of a job description for a compounding professional, see http://www.wedgewoodpharmacy.com/jobs/pharmacy-technician-general-compounding.html, accessed April 1, 2013.

[68] National Council of State Legislators, "State Regulation of Compounding Pharmacies," http://www.ncsl.org/issues-research/health/regulating-compounding-pharmacies.aspx. Telephone conversation between the author and Joe Cabaleiro, Executive Director, Pharmacy Compounding Accreditation Board, January 4, 2013; and, see American Pharmacists Association, "Frequently Asked Questions about Pharmaceutical Compounding," http://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding, accessed May 20, 2013.

[69] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington DC.

[70] Steven Galson, FDA, at a hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003, "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding." The FDA provided limited information on this study, so its reliability cannot be assessed.

[71] See J. Woodcock interview with an industry newsletter, Pharmalot: http://www.lawofcompoundingmedications.com/2013/04/during-pharmalot-interview-fda.html.

[72] See http://www.pharmacist.com/compounding-just-the-facts.

association representing the compounding profession, has 2,700 members.[73] As of January, 2013 there were 163 pharmacies in the United States accredited by the Pharmacy Compounding Accreditation Board, which offers a voluntary accreditation process for compounding pharmacies.[74]

Existing sources of publicly available information on specific CD products include those listed by compounding pharmacies on their websites,[75] products described by professional associations,[76] products mentioned in scientific journals, and on CDC and FDA websites due to warning and other notices.[77] These CDs include, among others, drugs for: pain management (including alternate delivery, combined medications, dosage variations), hormone replacement therapies for women (including bioidentical hormones) and men (e.g., testosterone), men's and women's health, sports medicine, weight-loss, dental care, veterinary care, pediatric patients, and hospice care.[78] Some compounded products include items advertised as treatments for Autism/ADHD,[79] "adrenal fatigue,"[80] or fat-elimination;[81] the FDA and others have raised questions regarding these claims.[82]

Non-Traditional Compounding

As noted earlier, some enterprises have engaged in certain activities not traditionally associated with compounding, but have asserted that these activities should be considered compounding.[83]

[73] See the International Academy of Compounding Pharmacies website, http://www.iacprx.org.

[74] Telephone conversation between the author and Joe Cabaleiro, Executive Director, Pharmacy Compounding Accreditation Board, January 4, 2013.

[75] Products provided by compounding pharmacies can be found on websites generated by standard searches of the web with keywords such as "compounding pharmacies." Further, the website of the Pharmacy Compounding Accreditation Board, a private non-profit organization that accredits compounding pharmacies has a list of accredited compounding pharmacies, http://www.pcab.org/. A list of products provided by compounded pharmacies can be found on the websites of accredited members, see for instance, CarePro Compounding. http://www.careprohs.com/pharmacies/compounding/ or A & O pharmacy, http://www.aopharmacy.com/compounding.html.

[76] Statement of K. Thompson, American Society of Health-System Pharmacists, hearing of Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 12, 2012, http://www.help.senate.gov/imo/media/doc/Thompson7.pdf.

[77] FDA Actions, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/#compliance See list of resources in CRS Report R42837, *Selected Resources on Federal Oversight of Compounding Pharmacies*, by (name redacted), (name redacted), and (name redacted) for examples of medical and scientific journals and FDA resources.

[78] For more information, see the following compounding pharmacies' websites: http://www.pccarx.com/join-pcca/; http://www.mooresphar macy.com/testimonials.htm; and http://www.hotzehwc.com/en-US/Treatment-Programs/FAQ.aspx.

[79] For example, see the following compounding pharmacy website: http://www.myvillagegreen.com/compounding-pharmacy/.

[80] For example, see the following compounding pharmacy http://www.hotzehwc.com/en-US/Treatment-Programs/Adrenal-Fatigue.aspx.

[81] In some instances the FDA has issued warning letters to compounding pharmacies regarding the claims of these products. For example, see FDA, "FDA Issues Warning Letters for Drugs Promoted in Fat Elimination Procedure," press release, April 7, 2010, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm207453.htm.

[82] "FDA Warns Marketers of Unapproved 'Chelation' Drugs, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm229358.htm; FDA Warning Letter CIN-10-94106-12, Libido Edge Labs, LLC, 06/10/2010; R. Sood et al., "Counseling Postmenopausal Women About Bio-Identical Hormones: Discussion Point 10: Adrenal Fatigue Does Not Mean Adrenal Insufficiency," *Journal of the Board of Family Medicine*, vol. 24, no. 2, (2011), pp. 202-210;

[83] See for instance, objections by compounding pharmacies to FDA regulation, including *Medical Ctr. Pharm.,* 536

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Such activities include the large-scale production of drugs to ease certain drug shortages, to meet outsourcing needs of hospitals and to supply physician-administered drugs.[84] Non-traditional compounders make a variety of products, including sterile injectables, parenteral nutrition, and drugs on the FDA shortage list.[85] Sterile injectable CDs include epidurals (for childbirth and pain management), nerve-blocking agents, drugs for pain management, and antibiotics.[86] Individuals might receive these products in a hospital, doctor's office, or other medical facility as a medication, an IV solution or nutrition.

Some non-traditional compounders have large numbers of customers. For example, PharMedium, a large scale compounder, reported 2,300 hospital customers for a variety of compounded products.[87] NECC, the compounder involved in the fungal meningitis outbreak of 2012, was listed on a FDA website as having over 20,000 customers, including physicians, clinics, and hospitals.[88]

Existing Regulatory Oversight

Drug compounding has historically been the focus of state governments through their regulation of pharmacies. Recently questions have arisen regarding the extent the federal government can regulate the practice of compounding through the FFDCA. This section discusses federal and state authorities, as well as industry self-regulation.

Federal Authorities[89]

Federal authority over compounding largely stems from the Federal Food Drug and Cosmetics Act (FFDCA), enacted in 1938, and its subsequent amendments, including the Food and Drug Administration Modernization Act (FDAMA) of 1997, which added compounding-specific

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F.3d and *Franck's Lab*, 816 F. Supp. 2d.

[84] The term "non-traditional" compounding is found in a number of sources: Comments of Margaret Hamburg, Commissioner of Food and Drugs, FDA, transcript of public meeting "Framework for Pharmacy Compounding: State and Federal Roles," December 19, 2012); Office of the Inspector General, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them*, Department of Health and Human Services, OEI-01-13-00150, Washington, DC, April 1, 2013. Another term used for this activity is "compounding manufacturing" (Source: S. 959 introduced by Senator Harkin and passed out of Committee by the Senate Committee on Health, Education, Labor and Pensions circulated in the 113th Congress).

[85] Parenteral nutrition is IV administered nutrition, which bypasses the digestive tract.

[86] See PharMedium, "Compounding Services," http://www.pharmedium.com/compounding/index.html, accessed May 20, 2013.

[87] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington DC, p. 7.

[88] See FDA http://www.fda.gov/downloads/Drugs/DrugSafety/FungalMeningitis/UCM325466.pdf, accessed May 20, 2013.

[89] Unless otherwise noted this section is based on CRS Report R43038, *Federal Authority to Regulate the Compounding of Human Drugs*, by (name redacted). For more information, see CRS Report R43038*Federal Authority to Regulate the Compounding of Human Drugs*, by (name redacted), and CRS Report R40503*FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

provisions to the FFDCA in Section 503A. Litigation over Section 503A's advertising provisions has created doubt, however, over the legal effect of FDAMA's compounding provisions.[90]

The precise limit to federal authority with respect to drug compounding remains uncertain as the federal authority to regulate traditional drug compounding has been discussed by very few courts, and each court that has approached the issue did so from a unique factual setting that colored the eventual outcome of the case.[91] Courts appear to agree that the federal government can regulate compounding activity that is akin to manufacturing (i.e., non-traditional compounding), and courts have afforded deference to the FDA's interpretation of when a compounder is acting like a manufacturer, which appears to be within the FDA's discretion.[92] However, there is not a bright-line distinction between behaviors that are "akin to manufacturing" and those of a traditional compounding pharmacy. As a result, uncertainty remains regarding the possible limits to the FDA's current authority to regulate traditional compounding practices.

Even assuming that FDA has the authority to regulate traditional compounding, as a matter of policy, the FDA has generally declined to test the current limits of its authority to regulate compounding, preferring instead to defer to state governments with respect to the regulation of "traditional compounding."[93]

State Authorities

Traditional compounding is a component of the practice of pharmacy and has typically been regulated by the states as "part of their regulation of pharmacies"[94] and the licensing of pharmacists as health care professionals.[95] There is great variety in existing state legislation addressing CDs.[96] Certain states have passed new laws, or are considering revisions of laws and regulations for compounding pharmacies, in part due to recent events.[97] The National Association of Boards of Pharmacies (NABP) has listed summaries of approved and proposed state changes to permitted compounding practices.[98]

State boards of pharmacy evaluate pharmacists and pharmacies on compounding practices and facilities.[99] Compounding from bulk ingredients is generally an approved part of pharmacy practice,[100] with some states requiring all licensed pharmacies to offer compounding services.[101]

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[90] Ibid., see the above reports for a discussion of Section 503A.

[91] See generally *Franck's Lab*, 816 F. Supp. 2d at 1235-1239 (discussing the cases that have examined the scope of the FDA's authority with respect to compounding).

[92] See e.g., *Wedgewood Village Pharmacy,* 421 F.3d at 272-73.

[93] *See* CPG §460.200 (May 29, 2002)*; see also* CPG §608.400 (July 14, 2003).

[94] *W. States Med. Ctr.*, 535 U.S. at 361.

[95] R.R. Abood, *Pharmacy Practice and the Law*, 6th ed. Sudbury, MA: Jones and Bartlett (2011).

[96] This report is not meant to be a comprehensive survey of state law regulations on pharmacy compounding. For more information on the topic, the National Conference of State Legislatures provides summaries of existing state laws and new initiatives. *See* "State Regulation of Compounding Pharmacies," updated April 13, 2013, http://www.ncsl.org/issues-research/health/regulating-compounding-pharmacies.aspx.

[97] Ibid.

[98] See National Association of Boards of Pharmacies, http://www.nabp.net/news/tagged/compounding.

[99] Ibid.

[100] See, e.g., Fla. Admin. Code Ann. 64B16-27.700(1)(c).

[101] See, e.g., 49 Pa. Code §27.18(p)(2); W. Va. Code St. Rules, tit. 15, §19.4.

Some states follow NABP model language and permit a pharmacist to compound drugs to patients only upon receipt of a valid prescription from a doctor or other medical practitioner licensed to prescribe medication.[102] Some states require a special license for compounding sterile medications, which requires special facilities and adherence to sterile methods.[103] Other states license a separate class of pharmacy facility that produces drugs for pharmacies or other providers, such as central fill pharmacies.[104] Finally, some states permit pharmacies to make exact copies of commercial products in response to discontinued products or drug shortages. [105]

Industry Self-Regulation

Professional programs in pharmacy are accredited and pharmacists generally receive formal education and professional training with respect to the practice of compounding drugs.[106] Pharmacists can participate in a voluntary accreditation process for compounding established by professional pharmacy organizations, and the U.S. Pharmacopeial Convention (USP). [107] As of December 2012, 163 facilities nationwide have this accreditation.[108]

Professional standards and guidelines for CDs are established by the USP in published standards: Chapter 797 "Pharmaceutical Compounding – Sterile Preparations" for sterile products and Chapter 795 "Pharmaceutical Compounding – Non-Sterile Preparations." USP Standard 797 includes standards for facilities, procedures, and staff in order to produce safe sterile drugs, such as sterilizing equipment, a sterile clean room, special ventilation, and decontamination processes.[109]

Not all pharmacies or compounders adhere to these USP standards and these standards, unless required by state law, are voluntary.[110] To date, 20 states have laws that require full adherence to USP Standard 797.[111]

USP standards are designed for pharmacy compounding and may not be suitable for large-scale production of CDs.[112] Commercial production of drugs is addressed by the current good

[102] See, e.g., Okla. Admin. Code §§535:15-10-3, 535:15-10-9(d); Colorado State Board of Pharmacy Rule 3.02.10.

[103] See for instance, California Business and Professional Code Section 4127 regarding standards for compounding injectable sterile products, http://www.leginfo.ca.gov/cgi-bin/displaycode?section=bpc&group=04001-05000&file=4127-4127.8, accessed May 21, 2013.

[104] See New Jersey 13:39-4.18(a) et seq. Procedures for Centralized Prescription Handling, http://www.njconsumeraffairs.gov/adoption/pharmado_100509.htm.

[105] See H.2. "The Pharmacy Act and Drug Control Act with Related Statutes", Commonwealth of Virginia, (July 1, 2012), http://www.dhp.virginia.gov/Pharmacy/pharmacy_laws_regs.htm.

[106] *W. States Med. Ctr.*, 535 U.S. at 361 (noting that as a "traditional component of the practice of pharmacy, compounding is taught as a part of the standard curriculum at most pharmacy schools.")

[107] The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured and distributed worldwide. USP's drug standards are referenced in FFDCA. The Pharmacy Compounding Accreditation Board (PBAB) sets standards for compounding, http://www.pcab.org/.

[108] See National Conference of State Legislatures, "State Regulation of Compounding Pharmacies, Updated April 16, 2013.

[109] See USP-NF, "General Chapter <797> Pharmaceutical Compounding – Sterile Preparations," (Date), Appendix A.

[110] Ibid., p. 9.

[111] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington DC, p. 8.

manufacturing practices (cGMP) required by Section 501 of the FFDCA for commercial manufacturers; cGMP requires certain manufacturing practices as well as adverse event reporting.[113]

Growth of Non-Traditional Compounding

Some believe that the number and types of CDs and other products (IV and parenteral nutrition) are increasing,[114] coinciding with increasing demand for certain compounded products[115] due to a variety of reasons, including (1) an increase in hospital outsourcing of CDs; (2) drug shortages, unavailability, and discontinuation of FDA-approved drugs;[116] (3) interest in individualized products by physicians and consumers; and (4) an increased interest by pharmacists in new markets.[117]

As noted earlier, the exact number of business facilities engaged in non-traditional compounding is unclear.[118] In 2013, the FDA inspected non-traditional compounding facilities that were engaged in sterile compounding and lists 39 facilities that it inspected located around the country.[119] Some of these facilities, such as Central Admixture Pharmacy Services and PharMEDium Services have multiple locations. Press and other sources indicate growth of centralized compounding facilities that provide outsourcing and related activities to pharmacies and hospitals.[120] Some of these compounding facilities include compounding pharmacies, central fill pharmacies,[121] and outsourcing pharmacies.[122] Some states, but not all, permit certain types of

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[112] Ibid.

[113] See also FDA "Facts About Current Good Manufacturing Practices" http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm.

[114] J. Lee, "Investors Buying Compounders," *ModernHealthcare.com*, January 19, 2013, http://www.modernhealthcare.com/article/20130119/MAGAZINE/301199973; F. Gebhart, "Flush with victory, compounding pharmacists see demand soar," *Drug Topics*, vol. 144, no. 2 (January 17, 2000), pp. 28-31; and testimony by Steven Galson, FDA, before the Senate Committee on Health, Education, Labor, and Pensions, October 23, 2003, http://www.fda.gov/NewsEvents/Testimony/ucm115010.htm.

[115] J. Lee, "Investors Buying Compounders," *ModernHealthcare.com*, January 19, 2013, http://www.modernhealthcare.com/article/20130119/MAGAZINE/301199973.

[116] E.S. Kastango, "Outsourced Medications: How Can You Know They Are Safe*?" Clinical IQ, 2013*, http://pharmacyonesource.com/images/simplifi797/Outsourcing-Meds.pdf.

[117] T. Mullarkey, "Considerations in Pharmacy Compounding and the Treatment of Spasticity, Introduction," *American Journal of Health-System Pharmacies,* vol. 66 (Suppl5), s2-3; V. Yancey et al., "Perceptions of Pharmaceutical Care Among Pharmacists Offering Compounding Services," *Journal of the American Pharmaceutical* Association, vol. 48, pp. 508-514 (2008); R. Jones, "Custom Cures," *Wayne State Alumni Magazine*, spring 2010, pp. 10-11, http://mydigimag.rrd.com/publication/index.php?i=37104&m=&l=&14&pre=&ver=swf&p=10; and Professional Compounding Centers of America, "Compounding and Pharmacists," http://www.pccarx.com/pharmacists/.

[118] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

[119] See FDA website "2013 Pharmacy Inspections," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm, accessed May 30, 2013.

[120] K. Kindy, L.H. Sun, and A. Crites, "Compounding pharmacies have been linked to deaths, illnesses, and safety failures for years," *Washington Post*, February 7, 2013, http://articles.washingtonpost.com/2013-02-07/national/36970682_1_medications-for-individual-patients-massachusetts-pharmacy-meningitis-outbreak; C. Lomax, "IV Outsourcing: Doing More with Less," White Paper, *Pharmacy Purchasing and Products*, http://www.pppmag.com/white_papers/.

[121] A central fill pharmacy is defined as a pharmacy which is permitted by the state in which it is located to prepare (continued...)

consolidated services, such as "shared services" or "central fill IV pharmacies,"[123] which make products for distribution among a variety of providers. For example, Med Prep Consulting, Inc. lists itself as a state-licensed central fill pharmacy and provides products to other pharmacies.[124]

Hospital Compounding and Outsourcing

Hospitals commonly compound drugs, IV solutions, and IV nutrition. For example, children's hospitals compound a variety of products such as pediatric dosages or products that are not commercially available.[125] One source reports that increases in use of drugs dosed by weight,[126] rather than in commercially-available dosing, and the expansion of treatment of disorders that require personalized dosing have led to a growth of hospital-based compounding.[127]

Trends in health care include increasing hospital consolidation and integration of hospitals,[128] leading to consolidated purchasing and centralized production, including the production of CDs.[129] For example, the Cleveland Clinic Health System, a network of 10 hospitals and 15 pharmacies, reported that in 2012, approximately 870,000 doses were compounded at its central facility.[130] Cleveland Clinic reported that 56% of its products were compounded for the needs of specific patients;[131] 44% were made in anticipation of patient needs in a large hospital, such as the preparation of syringes used in the operating room, epidurals, narcotic infusions, doses not

(...continued)

prescriptions on behalf of a retail pharmacy (pursuant to a valid prescription) to be distributed by the retail pharmacy to the patient if the two pharmacies have a contractual agreement. See for instance, 21 CFR 1300.01 "Definitions."

[122] "Outsourcing pharmacy" refers to the transmitting of a prescription order from a primary pharmacy to a secondary "outsourcing" pharmacy that prepares the prescription. See for instance: Maryland Office of the Secretary of State, http://www.dsd.state.md.us/comar/SubtitleSearch.aspx?search=10.34.04.

[123] See New Jersey 13:39-4.18(a) et seq. Procedures for Centralized Prescription Handling, http://www.njconsumeraffairs.gov/adoption/pharmado_100509.htm.

[124] FDA, "Medprep Consulting Inc. Announces Voluntary Nationwide Recall of all Lots of all Compounded Products Due To Potential Mold Contamination," March 17, 2013, http://www.fda.gov/Safety/Recalls/ucm344787.htm.

[125] Telephone conversation between author and Joe Cabaleiro, Executive Director, Pharmacy Compounding Accreditation Board, January 4, 2013. Recent amendments to the FFDCA require more extensive tests and labeling for prescription drugs for children. For more information about prescription drugs for children see CRS Report RL33986, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective*, by (name redacted), and CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144)*, coordinated by (name redacted).

[126] Such drugs include epidurals for pain management during childbirth or chronic pain conditions, and chemotherapy.

[127] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington DC, p. 5.

[128] Ibid., p. 4; K. Douglass and E.S. Kastango, "Consolidation of Pharmacy Compounding Services: An Alternative to Outsourcing," *International Journal of Pharmaceutical Compounding*, vol. 5, no. 2 (March/April 2001), pp. 140-144, http://www.clinicaliq.com/content/consolidation.pdf.

[129] Ibid. See also Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington, DC.

[130] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington, DC, p. 4.

[131] Products for an individual patient include anti-infectives, pain management therapies, chemotherapy drugs, replacement fluids and electrolytes, and ophthalmic preparations. See Pharmacy Compounding Summit: Summary of a Stakeholder Meeting, Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, February 6, 2013, Washington DC, p. 4.

commercially available, and medications that were unavailable due to drug shortages.[132] Smaller facilities in rural areas may increase the outsourcing of CDs due to need for specialty intravenous products without the facilities to produce such products.[133] Reductions in staff or insufficient staff or facilities to continue compounding; streamlining workflow; and cost savings may also be factors related to outsourcing by facilities.[134]

As noted earlier, there is limited information on the numbers of outsourced compounded products, as the records of compounding entities are not publicly reported. However, a 2013 report of the Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) on outsourcing of sterile products by hospitals found that 25% used "high-risk" sterile products, those made from non-sterile ingredients, while 92 % of hospitals used compounded sterile products that were not "high-risk".[135] The reasons hospitals provided for outsourcing sterile compounded products include drug shortages and their lack of capacity to produce products that remained stable over time and thus had a long shelf-life. Stability and extended shelf-life permit hospitals to store products for use as patient needs emerge. Shortages were cited as a reason for outsourcing by 62% of hospitals, as were stability (69%) and extended shelf-life (62%).[136]

The Role of Drug Shortages in CD Demand

Shortages of Generic Injectable Drugs

Shortages of commercially-available drugs, especially shortages of generic sterile products, play a central role in the increased demand for CDs.[137] The drug shortages may be temporary or permanent and are due to a variety of factors including voluntary discontinuation of products, supply chain problems, and production issues, including safety problems at commercial manufacturers.[138] Certain compounders advertise their ability to fill certain back-ordered drugs or

[132] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington, DC, p. 4.

[133]Ibid., p. 5, see text related to Prattville Baptist Hospital.

[134] See, C. Lomax, "IV Outsourcing: Doing More with Less," White Paper, *Pharmacy Purchasing and Products*, http://www.pppmag.com/white_papers/; Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington, DC, p. 5.

[135] Office of the Inspector General, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them*, Department of Health and Human Services, OEI-01-13-00150, Washington, DC, April 1, 2013, p. 4.

[136] Ibid., p. 6.

[137] E.S. Kastango, 2013; and C.Y. Johnson, "Compounding Pharmacies Fill Important Medical Niche," *Boston Globe*, November 3, 2012, http://www.bostonglobe.com/metro/2012/11/02/compounding-pharmacies-filled-niche-for-major-hospitals/47MsPtBMEkT67TQmfNXF8O/story.html; K. Fiore, "Drug Shortages Spark Use of Compounders," (October 18, 2012), http://www.medpagetoday.com/MeetingCoverage/ASA/35406; and T. Meyer, "Overseeing Outsourced Compounding During Shortages," *Pharmacy Purchasing and Products*, June 2012, http://www.pppmag.com/article/1141/June_2012/Overseeing_Outsourced_Compounding_during_Shortages/#.T9k83KBsIlQ.blogger; K. Thomas, "Lapses at Big Drug Factories Add to Shortages and Danger," *New York Times*, October 17, 2012, http://www.nytimes.com/2012/10/18/business/drug-makers-stalled-in-a-cycle-of-quality-lapses-and-shortages.html?pagewanted=all.

[138] K. Thomas, "Lapses at Big Drug Factories Add to Shortages and Danger," *New York Times*, October 17, 2012, http://www.nytimes.com/2012/10/18/business/drug-makers-stalled-in-a-cycle-of-quality-lapses-and-shortages.html?pagewanted=all.

those in short supply on their websites.[139] Shortages of commercially-manufactured drug are predicted to continue, leading to continued demand for certain compounded products.[140]

Physicians, hospitals, and other health care providers may turn to compounders to meet a time-sensitive need when specific drugs may be temporarily unavailable.[141] A 2013 report by the Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) surveyed hospitals participating in Medicare and found that many hospitals turn to compounding pharmacies to provide drugs to maintain supply due to shortages of commercially-manufactured FDA-approved drugs. According to the OIG report, 68% of hospitals indicated that they sought a CD due to a drug shortage.[142]

The FDA and other safety advocates are concerned because reportedly 73% of drug shortages are for sterile injectable generic drugs, which are some of the most difficult drugs to compound safely.[143] Several generic commercial manufacturers have struggled with manufacturing problems that have led to interruptions in supply of sterile generic drugs.[144] For example, as of May 15, 2013, a major generic manufacturer in this business sector, Hospira, has recalled eight different sterile injectable drugs for 2012 and 2013.[145] An alternative to sterile injectable CDs and generics are brand-name sterile injectables. These are less likely to be in short supply or suffer from

[139] See Wedgewood Pharmacy, "Drug Shortages and Alerts," http://www.wedgewoodrx.com/healthcare-professionals/current-drug-shortages-and-alerts.html, and http://www.wedgewoodpharmacy.com/news/press-room/wedgewood-pharmacy-compounds-gentamicin-as-sulfate-40mg-ml-injection-solution-during-manufacturer-.html, accessed April 1, 2013; Preckshot Professional Pharmacy http://www.preckshotpharmacy.com/rss2html.php?XMLFILE=http://www.pharmdjd.com/u/rss/meds_s.xml&TEMPLATE=unavailable_medications.html,accessed April 5, 2013; Universal Arts Pharmacy http://www.uaprx.com/, accessed April 5, 2013.

[140] J. Lee, "Investors Buying Compounders," ModernHealthcare.com, January 19, 2013, http://www.modernhealthcare.com/article/20130119/MAGAZINE/301199973; K. Fiore, "Drug Shortages Spark Use of Compounders," October 18, 2012, http://www.medpagetoday.com/MeetingCoverage/ASA/35406; and T. Meyer, "Overseeing Outsourced Compounding During Shortages," *Pharmacy Purchasing and Products*, June 2012, http://www.pppmag.com/article/1141/June_2012/Overseeing_Outsourced_Compounding_during_Shortages/#.T9k83KBsIlQ.blogger. Sections 1001-1008 of the Food Drug Safety and Administration Act (P.L. 112-144) included provisions to ease shortages, see FDA website http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm313121.htm.

[141] K. Thomas, "Drug Shortages Persist in U.S., Harming Care," *New York Times*, November 16, 2012, http://www.nytimes.com/2012/11/17/business/drug-shortages-are-becoming-persistent-in-us.html?pagewanted=all&_r=0&pagewanted=print; K. Fiore, "Drug Shortages Spark Use of Compounders," October 18, 2012, http://www.medpagetoday.com/MeetingCoverage/ASA/35406; and T. Meyer, "Overseeing Outsourced Compounding during Shortages," *Pharmacy Purchasing and Products*, June 2012, http://www.pppmag.com/article/1141/June_2012/Overseeing_Outsourced_Compounding_during_Shortages/#.T9k83KBsIlQ.blogger.

[142] Office of the Inspector General, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them*, Department of Health and Human Services, OEI-01-13-00150, Washington, DC, April 1, 2013.

[143] See comments of Margaret Hamburg, Commissioner of Food and Drugs, FDA, transcript of public meeting "Framework for Pharmacy Compounding: State and Federal Roles," December 19, 2012.

[144] See FDA Recalls: K. Thomas, "Lapses at Big Drug Factories Add to Shortages and Danger," *New York Times*, October 17, 2012, http://www.nytimes.com/2012/10/18/business/drug-makers-stalled-in-a-cycle-of-quality-lapses-and-shortages.html?pagewanted=all.

[145] See FDA Recalls: http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/.

quality problems;[146] however, brand-name sterile drugs usually cost more than generic or compounded products.[147]

Shortages of CDs

Recalls of products from compounding pharmacies may also exacerbate drug shortages.[148] Ameridose and NECC ended production of certain sterile drugs in 2012-2013 due to problems with sterility, and these drugs were already in short supply.[149] In 2013, compounders recalled certain products produced at these facilities;[150] some of these products were drugs listed on the FDA shortages website. For example, drugs recalled by Med Prep in March 2013 include drugs on the FDA Current Drug Shortage Index.[151]

CD shortages heighten problems of patient access to commercially-manufactured generic drugs when there are shortages. **Table 1** details the perceptions of hospitals about the effect of disruptions in supply of sterile products from compounding pharmacies. Almost 50% of respondents perceived that health care delivery would be seriously impacted, while 11.5% perceived that the effect on patient health would be life-threatening.

Table 1. Hospital Beliefs About The Effect of Shortages of Compounded Sterile Products on Patient Care and Health Care Delivery

Perceived Level of Risk to Patients/Disruption of Care	Percentage of Hospitals
Life Threatening/Major Disruptions	11.5
Not Life Threatening/Great Impact	48.1
Little Impact/Inconvenience	16.6
No Impact at All	23.8

Source: Adapted by CRS from Office of Inspector General, Department of Health and Human Services, Memorandum Report; "High Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them" OEI-01-13-00150, p. 14.

[146] J. Woodcock and M. Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," *Clinical Pharmacology and Therapeutics*," vol. 93, no. 2, (February 2013), pp.170-176.

[147] Ibid.

[148] E. Palmer, "Compounder Recall May Make Drug Shortages More Severe," *FiercePharmaManufacturing*, October 31, 2012, http://www.fiercepharmamanufacturing.com/story/compounder-recall-may-make-drug-shortages-more-severe/2012-10-31.

[149] K. Thomas, "Lapses at Big Drug Factories Add to Shortages and Danger," *New York Times*, October 17, 2012, http://www.nytimes.com/2012/10/18/business/drug-makers-stalled-in-a-cycle-of-quality-lapses-and-shortages.html?pagewanted=all.

[150] See FDA Drug Recalls, http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/.

[151] Compare FDA, "Drug Shortage Index," March 11, 2013, http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm, with list of drugs recalled by Med Prep, March 17, 2013, http://www.fda.gov/Safety/Recalls/ucm344229.htm.

Other Sources of Demand for Compounded Products

A growth of interest in customized products, including allergen-free drugs, single administration of multiple drugs, and individualized formulations of drugs (such as liquids instead of tablets) may play a role in heightened demand for CDs.[152] The sources of this demand include physician and patient demand as well as changing pharmacist business models. There appears to be an increase in marketing of CDs for treatment of common disorders, such as menopausal symptoms (e.g., "bio-identical" hormones), men's health, and weight loss, which may lead to an increase in demand for these CDs.[153] [154]

Pharmacist Business Development

Compounding may provide pharmacists alternatives to expand business growth. Pharmacy publications have emphasized how compounding pharmacists improve their own professional satisfaction through providing more individualized services and increased engagement with patients.[155] This reflects an evolution to business models that expand pharmacist roles in areas of patient care beyond distributing commercially-manufactured products.[156]

A 2012 article in *Business Week* describes drug compounding as a growing business sector, and describes how focusing on compounding can provide a new market niche for community pharmacies.[157] Some of these pharmacies may be exploring new business models due to increased competition with chain pharmacies and retailers to fill prescriptions for commercially-manufactured drugs. This account appears consistent with material on certain compounding pharmacies' websites that describe business development from community pharmacies into a market niche in compounded products (both prescription drugs and dietary supplements).[158]

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[152] E. Palmer, "Compounder Recall May Make Drug Shortages More Severe," *FiercePharmaManufacturing*, October 31, 2012, http://www.fiercepharmamanufacturing.com/story/compounder-recall-may-make-drug-shortages-more-severe/2012-10-31; Y. Johnson, "Compounding Pharmacies Fill Important Medical Niche," *Boston Globe*, November 3, 2012, http://www.bostonglobe.com/metro/2012/11/02/compounding-pharmacies-filled-niche-for-major-hospitals/47MsPtBMEkT67TQmfNXF8O/story.html.

[153] K. Cubert, "Compounding Pharmacies in the US: Doctor's orders: Drug Shortages and Demand from the Aging Population Will Benefit Stores," IBIS World Industry Report OD5706, May 2012, pp. 10-11; see also, FDA "How Widespread is the Marketing of Compounded "BHRT" drugs?"; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183088.htm; and a compounding pharmacy site, Precision Compounding Pharmacy: http://www.precisioncompoundingpharmacy.com/?q=bhrt.

[154] The FDA has issued warnings about the evidence of the usefulness or uniqueness of CDs for these indications. FDA, see "Bio-Identicals: Sorting Myths from Facts," http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049311.htm.

[155] V. Yancey et al., "Perceptions of Pharmaceutical Care Among Pharmacists Offering Compounding Services," *Journal of the American Pharmacists Association*, vol. 48, no. 4 (Jul/Aug 2008), pp. 508-514; and R. Jones, "Custom Cures," *Wayne State Alumni Magazine*, spring 2010, pp. 10-11, http://mydigimag.rrd.com/publication/index.php?i=37104&m=&l=&14&pre=&ver=swf&p=10.

[156] See for instance. Chain Drug Review, "2012 Retail Forecast: Chain Drug Eyes Broader Role," http://www.chaindrugreview.com/inside-this-issue/news/01-02-2012/2012-retail-forecast-chain-drug-eyes-broader-role; Council on Credentialing in Pharmacy, "Scope of Contemporary Pharmacy Practice: Roles, Responsibilities, and Functions of Pharmacists and Pharmacy Technicians, *Journal of the American Pharmacy Association*, vol. 50, no. 2 (March-April, 2010), e35-e69.

[157] P.M. Barrett, "America's shadow pharmacies," *Business Week*, http://www.businessweek.com/articles/2012-11-14/americas-shadow-pharmacies.

[158] For instance, see Kelley Ross https://www.krrph.com/about-us/history.aspx, accessed March 31, 2013.

Provider Demand

Demand may be generated in part by off-label prescribing by physicians for a variety of reasons, including drug prices and shortages. As **Table C-1** indicates, some of the incidents of contamination and adverse events are for CDs prescribed for off-label uses. Off-label prescribing allows physicians flexibility to prescribe medications they feel are necessary for patient health.[159] Off-label use of a CD may present additional, but unknown risks. For example, two common off-label uses of sterile CD are a compounded version of a chemotherapy drug, Avastin, for use to treat macular degeneration, and preservative-free methylprednisolone for back pain.[160] There have been recent adverse events with compounded Avastin, the main appeal of which is its lower price compared to FDA-approved drugs to treat macular degeneration (see **Table C-1**, 2011).[161] Preservative-free methylprednisolone is used to treat back pain (see **Table C-1**, years 2013, 2012, 2002, 2001). Compounded versions of this drug by NECC were the cause of the 2012 fungal meningitis outbreak.[162]

The processes for creating sterile CDs require special equipment, facilities, and personnel training.[163] When compounding exclusively with sterile ingredients, sterility must be maintained in all phases of production; when compounding with non-sterile ingredients, sterility must be achieved for the finished product requiring a sterilization process or related procedure that does not affect product stability. Regulators and industry agree that the highest risk to patient safety is from those sterile products made from non-sterile ingredients.[164]

Issues for Consideration

Consumers, pharmacists, pharmacy compounders, hospitals, Congress, and state and federal regulators all have a stake in access to, and safety of, needed drugs. Increasing demand for CDs by patients and providers, drug shortages, consolidation of hospital services and other factors have led to changes in health delivery. The potential risks to public health of product failures have

[159] Ibid., and R. Dresser & J. Frader, "Off-label prescribing: A Call for Heightened Professional and Governmental Oversight," *Journal of Law and Medical Ethics*, vol. 37, no. 3, pp. 476-486.

[160] R. Lowes, "Compounding Pharmacy Crackdown Continues with Avastin Recall," http://www.medscape.com/viewarticle/781039 accessed May 20, 2013; J. B. Staal et al., "Injection therapy for subacute and chronic low back pain: An updated Cochrane Review," *Spine*, vol. 34, no. 1 (January 2009), pp. 49-59. Evidence differs on whether these off-label treatments are effective.

[161] Ibid.

[162] See CDC, *Multistate Fungal Meningitis Outbreak Investigation - Current Situation*, http://www.cdc.gov/HAI/outbreaks/currentsituation/.

[163] See T. Mullarkey, "Pharmacy Compounding of High-Risk Products and Patient Safety," *American Journal of Health-System Pharmacists*, vol. 66 (Suppl5), (September 1, 2009), p. s5; see USP-NF, "General Chapter <797> Pharmaceutical Compounding – Sterile Preparations," http://www.usp.org/store/products-services/usp-compounding.

[164] Office of the Inspector General, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals that Use Them*, Department of Health and Human Services, OEI-01-13-00150, Washington, DC, April 1, 2013; "FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety and Effectiveness," updated 04/20/2009, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm; comments of Margaret Hamburg, Commissioner of Food and Drugs, FDA, transcript of public meeting "Framework for Pharmacy Compounding: State and Federal Roles," December 19, 2012, pp. 10; and see USP-NF, "General Chapter <797> Pharmaceutical Compounding – Sterile Preparations," http://www.usp.org/store/products-services/usp-compounding.

increased as non-traditional compounding has expanded.[165] Given the expansion of sterile compounding, balancing patient access to CDs with patient safety has become more complex.[166] Thus, some stakeholders believe that changes in business trends, such as drug shortages and outsourcing of compounding, must be taken into consideration in considering changes in professional standards and federal and state oversight and regulation of CD.[167]

Three issues have emerged in the congressional hearings about CDs and in legislation introduced in the 112th and 113th Congress (see **Table A-1**): (1) adverse event reporting, (2) labeling, and (3) modifying federal oversight of non-traditional compounding. These issues will be discussed in the following section.

Adverse Event Reporting and Labeling

There is a lack of publically available information on the number and types of adverse events involving compounded drugs, as there is no requirement that compounders report adverse events to federal authorities,[168] and state requirements vary.[169] Adverse event reporting is not required by federal regulators for producers of CDs as it is for prescription, non-prescription drugs, and dietary supplements.[170] Without knowing the total number of compounded products made, as well as the total number of adverse events, it is difficult to ascertain the overall safety of CDs or to understand the benefits and risks of using CDs.

The publicly-available information on CDs is published by public health authorities, FDA inspections of facilities listed on websites, records of state licensing boards, and reports in professional journals documenting adverse events. Adverse events can be voluntarily reported to

[165] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013, http://www.help.senate.gov/hearings/hearing/?id=f9b68c5e-5056-a032-52b6-4e632afd726a.

[166] For more information, see hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013, http://www.help.senate.gov/hearings/hearing/?id=f9b68c5e-5056-a032-52b6-4e632afd726a.

[167] See statements and response to questions of Panel 2 at "Pharmaceutical Compounding: Proposed Legislative Solution," a hearing of the Senate Committee on Health, Education, Labor and Pensions, May 9, 2013, http://www.help.senate.gov/hearings/hearing/?id=f9b68c5e-5056-a032-52b6-4e632afd726a.

[168] Adverse events are reported to poison control centers, FDA, CDC, or state public health authorities. Adverse event reporting is required for commercially-manufactured drugs (21 U.S.C. §355-1), non-prescription drugs (21 U.S.C. §379aa), and dietary supplements (21 U.S.C. §379aa-1); for more information see, CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by (name redacted) and CRS Report R43025, *FDA Regulation of Dietary Supplements*, by (name redacted). Also see Guidance for Industry http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299138.pdf; FDA Adverse Event Reporting System http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.htm.

[169] A few, but not all, states require some form of reporting of adverse incidents from CDs, see National Council of State Legislators, "State Regulation of Compounding Pharmacies," http://www.ncsl.org/issues-research/health/regulating-compounding-pharmacies.aspx; see for instance, Massachusetts http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/121101-pharmacy-board-draft-emergency-regs.pdf, and Texas http://law.onecle.com/texas/occupations/562.153.00.html.

[170] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

the FDA MedWatch database, but without mandatory reporting, the completeness of the information cannot be ascertained.[171]

Labeling specifying that a drug or another product is compounded is not a universal requirement.[172] Due to the complexity of the supply chain and the growth of non-traditional compounding, patients and providers may not realize that a drug has been compounded. Unlike traditional compounding where a patient is given a prescription by a physician for a CD, non-traditional CDs are not necessarily identified as compounded.[173] Given the potential benefits and risks of CDs, an argument could be made for providing patients this information as part of informed consent for medical treatment.[174] Informed consent for treatment is an ethical and a legal requirement to ensure that a patient fully understands the potential risks and benefits of a medical procedure.[175] CDs and other compounded solutions pose potential risks and benefits that may be different from commercially-manufactured products. Informed consent is based on a patient's knowledge and understanding of a medical procedure; as most patients assume that drugs are commercially-manufactured, this additional information could be seen as necessary to the ethical pursuit of informed patient consent.[176]

The Federal Role in Oversight

Policymakers have raised questions regarding how best to improve the safety of CDs while maintaining patient access to needed medications, including the need for new legislation and increased accountability. [177] In testimony to Congress, FDA administrators have expressed reservations about non-traditional compounding activities that are akin to manufacturing (i.e.,

[171] See http://www.fda.gov/Safety/MedWatch/default.htm.

[172] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013. H.R. 6584and H.R. 6638 were introduced in the 112th Congress. In the 113th Congress, S. 959 was introduced by Senator Harkin. An Executive Committee hearing was held and the legislation in the 113th Congress by Representative Markey; this bill includes provisions that provide for patient information on whether a drug is compounded in labeling.

[173] Statement and response to questions, Janet Woodcock, FDA at a hearing of the Senate Committee on Health, Education, Labor and Pensions, "Pharmaceutical Compounding: Proposed Legislative Solution," May 9, 2013.

[174] See for instance "Pharmacy Compounding: Facts and Information," specifically "When Are Compounded Drugs Necessary," and "Disclosure" http://www.ppsinc.org/phcom/03risk.htm; and M. R. Cohen, "New legislation would help users identify source of a compounded drug," *Philly.com*, http://www.philly.com/philly/blogs/healthcare/New-legislation-would-help-users-identify-source-of-a-compounded-drug.html#D0rsmdaRGFqMCMWT.99.

[175] T. L. Beauchamp and J. F. Childress, *Principles of Biomedical Ethics*, 9th ed. (New York: Oxford University, 2009).

[176] See for instance "Pharmacy Compounding: Facts and Information," specifically "When Are Compounded Drugs Necessary," and "Disclosure" http://www.ppsinc.org/phcom/03risk.htm; and M. R. Cohen, "New Legislation Would Help Users Identify Source of a Compounded Drug," *Philly.com*, http://www.philly.com/philly/blogs/healthcare/New-legislation-would-help-users-identify-source-of-a-compounded-drug.html#D0rsmdaRGFqMCMWT.99.

[177] See transcripts of: "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, April 26, 2013; "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 15, 2012; "The Fungal Meningitis Outbreak: Could It Have Been Prevented?" hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 14, 2012; "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding." hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003.

non-traditional compounding) and their potential risks to public safety.[178] The FDA recommends increased federal oversight of sterile compounding and certain other high-risk activities.[179]

Attempts to clarify federal authority over non-traditional compounding is represented in certain elements of bipartisan legislation of the Senate Committee on Health, Education, Labor and Pensions (HELP)[180] and in legislation introduced in the 112th and 113th Congress.[181] These proposals all include increased clarity in the federal oversight role for compounding drugs. For example, a provision in the draft HELP legislation would create new authorities for FDA oversight of "compounding manufacturers" (i.e., non-traditional compounders) (see **Table A-1**).[182]

Some Members of Congress argue that new FDA authorities should await better implementation of existing authorities.[183] For example, a House Committee on Energy and Commerce report questions whether a lack of enforcement by FDA and state authorities of certain vendors is an issue.[184] The report cites safety violations at NECC in prior years, which do not appear to have been resolved despite FDA involvement.[185]

Some in the compounding pharmacy industry believe that the current safety issues are isolated to certain vendors and that compounding, in general, is not unsafe.[186] Some compounding associations have reservations about the FDA having new authorities; others support increased FDA oversight.[187] Many acknowledge that compounded health care products have become more

[178] For instance, see Testimony of Margaret Hamburg, Commissioner of Food and Drugs, before the Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 15, 2012, http://www.fda.gov/NewsEvents/Testimony/ucm327667.htm; Statement of Margaret Hamburg before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 14, 2012, http://www.fda.gov/NewsEvents/Testimony/ucm327664.htm; and, Steven Galson, FDA, at a hearing of the Senate Committee on Health, Education, Labor, and Pensions, 108th Congress, 1st Session, October 22, 2003, "Examining State and Federal Oversight to Ensure the Safety and Quality of Drug Compounding."

[179] Ibid.

[180] See S. 959 introduced by Senator Harkin and passed out of the Senate Committee for Health, Education, Labor, and Pensions.

[181] See H.R. 6584 introduced by Representative Markey and H.R. 6638 introduced by Representative DeLauro in the 112th Congress, and H.R. 2186 introduced by Representative Markey in the 113th Congress.

[182] See S. 959 introduced by Senator Harkin and passed out of the Senate Committee for Health, Education, Labor, and Pensions.

[183] U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, *Majority Memorandum RE: Hearing on "The Fungal Meningitis Outbreak: Could It Have Been Prevented?",* November 12, 2012 and "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, April 26, 2013.

[184] U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, *Majority Memorandum RE: Hearing on "The Fungal Meningitis Outbreak: Could It Have Been Prevented?",* prepared by Subcommittee on Oversight and Investigations Staff, 112th Cong., 2nd sess., November 12, 2012, pp. 25, http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/Hearings/OI/20121114/HMTG-112-HHRG-IF02-20121114-SD001.pdf.

[185] Ibid., pp. 6-23.

[186] Testimony from David Miller, International Academy of Compounding Pharmacists, Committee on Health, Education, Labor, and Pensions, "Pharmacy Compounding Implications of the 2012 Meningitis Outbreak," November 15, 2012, http://www.help.senate.gov/imo/media/doc/Miller8.pdf.

[187] See Panel II statements and response to questions, "Pharmaceutical Compounding: Proposed Legislative Solution," a hearing of the Committee on Health, Education, Labor, and Pensions, May 9, 2013; Press Release, PharMedium, (continued...)

complex and health delivery more complicated. In a recent report, the Association of Health-System Pharmacists (AHSP) and American Hospital Association (AHA) noted that there was general support from stakeholders in these associations for (1) FDA oversight of certain non-traditional compounding pharmacies (e.g., providing a CD without a prescription and shipped over state lines); (2) improved communication between state and federal regulators; (3) a list of "do-not-compound" CDs; and (4) improved access to USP compounding monographs that provide guidance to compounders on making certain CDs.[188]

(...continued)

March 26, 2013, http://www.lawofcompoundingmedications.com/2013/03/pharmedium-supports-new-fda-category.html, accessed May 3, 2013.

[188] Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, "Pharmacy Compounding Summit: Summary of a Stakeholder Meeting," February 6, 2013, Washington DC, p. 14.

Appendix A. Legislation Introduced in the 113th Congress Affecting Drug Compounding

The following table summarizes selected provisions of the two pieces of legislation on compounding introduced to date in the 113th Congress. It includes provisions that address issues discussed in this report, but it does not provide a full summary of the legislation.

Table A-1. Selected Issues in S. 959 and H.R. 2186

Issues	S. 959 *Bill Status: Committee Actions: Ordered to be Reported*	H.R. 2186 *Bills Status: Introduced*
Adverse Event Reporting	Yes	Yes
Federal Authorities	(1) Would clarify that a "new drug" (Section 201(p) of the FFDCA) includes compounded human drugs; (2) contains specific provisions regarding "traditional compounders" and "compounding manufacturers."	Provides that certain adulteration and misbranding provisions of the FFDCA and the "new drug" provisions of the FFDCA do not apply to certain compounded drugs.
Federal Registration of Certain Compounders	Yes	Yes
Labeling	Would require specific labeling as compounded drug, among other requirements. Drug would be considered misbranded (and would be subject to penalties) under FFDCA if not so labeled.	Would require specific labeling as compounded drug, among other requirements. Drug would be considered misbranded (and would be subject to penalties) under FFDCA if not so labeled.
Registration of Compounders	Yes, fee would be required to off-set costs of inspection and oversight.	Yes, fee would be required to off-set costs of inspection and oversight.
Shortages	Would permit copies of FDA-approved drugs during verified shortages.	Would permit copies of FDA-approved drugs during verified shortages.
Special Rules for Sterile Compounding	Yes, would clarify FDA oversight regarding sterile manufacturers who ship across state lines, and would create new manufacturing standards for these products.	Yes, would create new manufacturing standards for "high-risk" sterile compounding.

Source: CRS review of legislation: S. 959 ; H.R. 2186.

Note: FFDCA is the Federal Food, Drug, and Cosmetic Act as amended (21 U.S.C. §301 et seq.).

Appendix B. Congressional Hearings on CDs 2012-2013 (in Reverse Chronological Order)

- "Examining Drug Compounding," hearing of the Subcommittee on Health of the Committee on Energy and Commerce, U.S. House of Representatives, May 23, 2013.
- Executive Session, S. 959 Pharmaceutical Compounding Quality and Accountability Act, hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, May 22, 2013. Ordered to be reported with an amendment in the nature of a substitute favorably.
- "Pharmaceutical Compounding: Proposed Legislative Solution," hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, May 9, 2013.
- "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, April 26, 2013.
- "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," hearing of the Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 15, 2012.
- "The Fungal Meningitis Outbreak: Could It Have Been Prevented?", hearing of the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 14, 2012.

Source: House Committee on Energy and Commerce: http://energycommerce.house.gov/hearings; Senate Committee on Health, Education, Labor and Pensions: : http://www.help.senate.gov/hearings/.

Appendix C. Selected Adverse Events Involving Compounded Drugs and Solutions

Table C-1. Adverse Events

2001-May 30, 2013

Date	# States Affected	Reported Cases	Reported Deaths	Adverse Events	Drug Issue	Condition/ Disease Treated	Product	Other Characteristics
2013	13	7	0	Skin abscess, including fungal infection	Contamination[a]	Lumbar and other back pain	Lumbar and other back pain	Off-label use, shipped across state lines
2012	20	741	55	Fungal meningitis and other infections[b]	Fungal contamination	Lumbar and other back pain	Lumbar and other back pain	Off-label use, shipped across state lines, drug shortage
2012 -2011	6	33	NA	Fungal eye infection, 23 cases of partial to severe vision loss[c]	Fungal contamination	Eye surgery	Eye injections, Brilliant B retinal dye and triamcinolone	Shipped across state lines
2011	2	21	NA	Bacterial eye infection, one case of meningitis and encephalitis; four cases of loss of eyesight, 3 cases eye removal[d]	Bacterial contamination	Macular degeneration	Eye injections: Intravitreal use of bevacizumab (Avastin) injections	Off-label use, shipped across state lines
2011	1	5	NA	Blindness[e]	Lack of purity – presence of another medication	Macular degeneration	Eye injections: intravitreal use of bevacizumab (Avastin) injections	Off-label use
2011	1	19	9	Bacterial bloodstream infection[f]	Bacterial contamination	Nutrition	Parenteral nutrition solution	Drug Shortage
2010	1	1	1	Fatal overdose[g]	Super-potent dosage	IV solution	Sodium chloride	- -
2007	2	3	3	Fatal overdose[h]	Super-potent dosage	Back pain	Colchicine	Off-label use
2007	2	8	NA	Bacterial bloodstream infection[i]	Bacterial contamination	Pain control	IV-solution, fentanyl	Shipped across state lines
2007	*1*	*1*	*1*	*Drug toxicity[j]*	*Drug Stability/Age*	*Chronic airway infection*	*Antibiotic administered by nebulizer*	*Off-label use*

Date	# States Affected	Reported Cases	Reported Deaths	Adverse Events	Drug Issue	Condition/ Disease Treated	Product	Other Characteristics
2006-2004	6	80	NA	Bacterial bloodstream infection[k]	Bacterial contamination	IV flush, reduction of blood clots	IV solution heparin/saline	Shipped across state lines
2006	1	1	1 (pediatric)	Fatal overdose[l]	Super-potent dosage	Cancer	Chemotherapy infusion	- -
2006	1	1	1 (pediatric)	Fatal overdose[m]	Super-potent dosage	Nutrition	Parenteral nutrition	- -
2005	Unavailable	2	NA	Bacterial bloodstream infection[n]	Bacterial contamination	IV flush	Preservative-free heparinized saline	- -
2005	1	5	3	Systemic inflammatory response syndrome[o]	Contamination	Cardiac conditions	Health infusion, cardioplegia	Shipped across state lines
2005	2	6	NA	Bacterial eye infection, partial or complete loss of vision, 2 eye removals[p]	Bacterial contamination	Assessment of eye conditions	Trypan blue – eye stain	Shipped across state lines
2005	5	18	NA	Bacterial bloodstream infection[q]	Bacterial contamination	IV solution	Magnesium sulfate	Shipped across state lines
2004	1	2	NA	Bacterial bloodstream infection (pediatric)[r]	Bacterial contamination	IV flush syringes	Heparin/vancomycin, hemophilia	Shipped across state lines
2004	5	64	NA	Bacterial bloodstream infection[s]	Bacterial contamination	IV flush syringes	Heparin/saline	Shipped across state lines
2004	*1*	*16*	*NA*	*Hepatitis C infection[t]*	*Contaminated with Hepatitis C virus*	*Diagnosis of cardiac conditions*	*Radio-isotope use in cardiac stress tests*	- -
2002	1	5	1	Fungal meningitis[u]	Fungal contamination	Back pain	Preservative-free methylprednisolone acetate injections	Off-label use, drug shortage
2001	1	11	3	Bacterial meningitis, epidural abscess, injected joints and spine[v]	Fungal contamination	Back pain, joint pain	Preservative-free betamethasone injection	Off-label use, drug shortage
2001	1	4 (pediatric)	NA	Bacterial meningitis, other infections[w]	Bacterial contamination	Gastric reflux	IV Ranitidine	- -

Source: This list has two sources (1) a CRS literature search of medical and scientific databases such as Medline and PubMed with search terms included "drug compounding," and "adverse effects," "quality control," "risk assessment," "drug contamination," "disease outbreaks," "complications," "administration and dosage," "fatal outcome," and "medication errors." These selected adverse events resulted in reported patient illness and/or death. This is list is not comprehensive as not all adverse effects of compounded medications may be reported to federal and state authorities or result in published articles; (2) Pew Charitable Trust compilation of

adverse events associated with compounded medications (2001-present), Appendix B of Summary of Stakeholder Meeting, Pharmacy Sterile Compounding Summit. Available at http://www.ashp.org/compounding%20summit, accessed April 18, 2012. The CRS and Pew Trust lists overlap except for two adverse events that are included only in this report; these two events are italicized.

Notes: "NA" means not applicable. "Unknown" means not included in source document. Off-label use of a prescription drug or device refers to the ability of licensed health care providers to prescribe or use the drug for indications, conditions, patients, dosages or routes of administration not yet evaluated and approved by the FDA as part of a new drug approval application. Drug Shortage designation is based on either a specific discussion of those issues in the article or a third-party source, such as the FDA, the American Health-System Pharmacists or professional article. Specific sources for the reports of adverse events are listed below:

a. Information is still emerging about this incident and the information listed here is incomplete.

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