Selected Resources on Federal Oversight of Compounding Pharmacies

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In September 2012, the Centers for Disease Control and Prevention (CDC), the Tennessee Department of Health, the Food and Drug Administration (FDA), and other state health departments[1] began investigating a rare, non-contagious[2] outbreak of fungal meningitis. As of March 4, 2013, 20 states have reported 720 infections (including fungal meningitis and other conditions) and 48 deaths.[3] Patients at risk are those who received injections of contaminated, preservative-free methylprednisone acetate produced by the New England Compounding Center (NECC) after May 2012.[4] On October 4, 2012, the FDA verified that NECC was the source of the contaminated products.[5]

There has been extensive news coverage of the outbreak, which raised issues about the safety of compounded drugs and the role of federal and state governments in regulating compounded drugs and compounding pharmacies.[6] A number of policy questions about FDA authority and resources were raised in congressional hearings held by the Energy and Commerce Committee of the U.S. House of Representatives and the Health, Education, Labor, and Pensions Committee of the U.S. Senate.[7]

This report provides selected resources on the federal government's oversight of compounded drugs and compounding pharmacies, with an emphasis on relevant federal law and regulation and

[1] 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, *Multistate Fungal Meningitis Outbreak—Current Case Count*, http://www.cdc.gov/hai/outbreaks/meningitis.html.

[4] Centers for Disease Control and Prevention, *Multistate Fungal Meningitis Outbreak*, http://www.cdc.gov/HAI/outbreaks/currentsituation/.

[5] 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.

[6] Lena H. Sun and Kimberly Kindy, "FDA inspects specialty compounding pharmacies in targeted action," *Washington Post,* March 1, 2012, http://articles.washingtonpost.com/2013-03-01/national/37368259_1_pharmacies-drug-evaluation-inspection; Kimberly Kindy, Lena H. Sun, and Alice 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; Andrew Pollack and Sabrina Tavernise, "Oversight Failures Documented in Meningitis Outbreak," *New York Times*, November 21, 2012, http://www.nytimes.com/2012/11/22/health/documents-show-fdas-failures-in-meningitis-outbreak.html; Denise Grady, "Deaths Stir a Dispute on Powers of FDA," *New York Times*, November 20, 2012, http://www.nytimes.com/2012/11/20/health/tainted-drug-deaths-spawn-heated-debate-over-fdas-powers.html?ref=health&_r=0; Sabrina Tavernise, "FDA Chief Seeks Expanded Authority to Improve Safety of Drug Compounders," *New York Times*, November 14, 2012, http://www.nytimes.com/2012/11/15/health/fda-asking-for-more-control-over-drug-compounding.html?ref=health; and Eric Lichtblau and Sabrina Tavernise, "Friends in Congress Have Helped Drug Compounders Avoid Tighter Rules," *New York Times*, November 13, 2012, http://www.nytimes.com/2012/11/14/health/niche-drugmakers-get-help-on-capitol-hill.html?pagewanted=all&_r=0.

[7] U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, *The Fungal Meningitis Outbreak: Could It Have Been Prevented*, 112th Cong., 2nd sess., November 14, 2012, http://search.proquest.com/docview/1151991974/13AA2A2331776953950/1?accountid=41647. U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak*, 112th Cong., 2nd sess., November 15, 2012, http://www.help.senate.gov/hearings/hearing/?id=5f5def0d-5056-a032-5297-eab57634d209.

the activities of federal agencies related to and following the 2012 fungal meningitis outbreak. Resources from three states that have direct roles in this outbreak through licensing NECC, or reporting and tracking the fungal meningitis outbreak, are included as well. After a brief background section, the selected resources presented in this report appear in the following order:[8]

- federal law;
- congressional hearings;
- proposed legislation (current and previous Congresses);
- congressional support agency products;
- FDA agency guidance and regulations, meetings, and related documents;
- FDA actions on drug compounding;
- other federal agency actions and resources;
- selected state resources; and
- articles from legal, professional, and scientific journals.

Background[9]

Drug compounding is a process in which a pharmacist combines, mixes, or alters various drug ingredients to create a medication for an individual patient in response to a practitioner's prescription.[10] It is generally used to prepare medications that are not typically commercially available, such as a drug in a lower dosage for a child, or a drug without a dye or a preservative in response to a patient allergy.[11] Compounding is a component of the practice of pharmacy and has historically been regulated at the state level, along with the licensure of pharmacy professionals and the regulation and licensure of pharmacies.[12]

The FDA is a regulatory agency within the Department of Health and Human Services (HHS). A key FDA responsibility, under the Federal Food, Drug, and Cosmetic Act (FFDCA), is the regulation of the safety and effectiveness of drugs sold in the United States.[13] Notwithstanding

[8] Articles or sources listed in this report are available from the Congressional Research Service. Please contact (name redacted), 7-.....

[9] This section relies on CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

[10] Food and Drug Administration, "Pharmacy Compounding," page last updated March 1, 2013, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm. ; and see also Western States Medical Center v. Shalala, 238 F.3d 1090, 1092 (9th Cir. 2001).

[11] Western States Medical Center et al. v. Shalala, 69 F. Supp. 2d 1288, 1292 (D. Nev. 1999). See also Statement of Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, before the Senate Committee on Health, Education, Labor, and Pensions, hearing on "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients," (Oct. 23, 2003).

[12] 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; and Western States Medical Center et al. v. Shalala, 69 F. Supp. 2d 1288, 1292 (D. Nev. 1999).

[13] For more information about the FDA's responsibilities with regard to prescription drugs, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by (name redacted).

state regulation of pharmacies and the practice of pharmacy, the "FDA has determined that it should seriously consider enforcement action" over activities of a compounding pharmacy "when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act [FFDCA]."[14] The recent FDA activities related to the fungal meningitis outbreak are not its first related to drug compounding. In the past the FDA has addressed the compounding of specific drugs (e.g., hormone replacement therapies for women, Makena, and colchicine[15]) and contamination of compounded drugs.[16] The next sections detail the existing federal role with regard to compounded drugs and compounding pharmacies.

Federal Law

Congress moved to clarify the FDA's role in the regulation of drug compounding by adding Section 503A (21 U.S.C. 353a) to the FFDCA as part of the FDA Modernization Act of 1997 (FDAMA, P.L. 105-115). Section 503A exempts compounded drugs from FFDCA requirements regarding drug adulteration, misbranding, and new drug approval process, provided that certain conditions are satisfied.[17] Specifically, a drug product must be compounded by a licensed pharmacist or physician for an identified individual patient based on a valid prescription that was not solicited.[18] The compounded drug must comply with certain U.S. Pharmacopoeia standards or a relevant national formulary monograph, or be made from FDA-approved drug ingredients, and must meet certain manufacturing criteria.[19] The drug compounded must not be one that appears on a list of drugs or drug products (published by the Secretary of HHS) that have been withdrawn or removed from the market because the product or components of the product have been found to be unsafe or not effective.[20] Finally, the drug compounder may not "compound regularly or in inordinate amounts … any drug products that are essentially copies of a commercially available drug product."[21]

Section 503A of FFDCA also states that a drug may be compounded and subject to the exemptions only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug.[22] This was challenged by several compounding pharmacies as an impermissible regulation of speech under the First Amendment. The case went to the 5th and 9th Courts of Appeals and eventually to the U.S. Supreme Court, which agreed that the regulation was unconstitutional as it was not a permitted restriction of speech.[23] Whether the

[14] See section identified as "Policy" in Food and Drug Administration, *Pharmacy Compounding: Compliance Policy Guidance*, CPG Sec. 460.200, Washington, DC, May 2002, http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm.

[15] Makena is a product that is used to reduce the risk of preterm birth and colchicine is a drug used to treat gout.

[16] For more information, see "FDA Actions on Drug Compounding."

[17] See Section 127 of P.L. 105-115 (FFDCA 503A).

[18] 21 U.S.C. §353(a)

[19] 21 U.S.C. §353a(b)(1).

[20] 21 U.S.C. §353a(b)(1).

[21] 21 U.S.C. §353a(b)(1)(D).

[22] 21 U.S.C. §353a(c).

[23] Western States, 535 U.S.357 (2002).

rest of the provisions of Section 503A are severable from the free speech provision, and are thus binding, is uncertain.[24]

- **FFDCA Section 503A** (21 U.S.C. 353a), Food and Drugs, Drugs and Devices: Pharmacy Compounding, http://www.gpo.gov/fdsys/pkg/USCODE-2011-title21/pdf/USCODE-2011-title21-chap9-subchapV-partA-sec353a.pdf.
- Specifics regarding Congressional intent during consideration of this issue can be found in Senate Committee on Labor and Human Resources report, S.Rept. 105-43, *Food and Drug Administration Modernization and Accountability Act of 1997*, S. 830, 105th Cong., 1st sess., July 1, 1997, pp. 67-69, http://www.gpo.gov/fdsys/pkg/CRPT-105srpt43/pdf/CRPT-105srpt43.pdf.

Section 510 of FFDCA requires the registration of establishments involved in the manufacture, propagation, compounding, or processing of a drug or drugs; however, it specifically excludes pharmacies functioning in conformance with local laws.

- **FFDCA Section 510** (21 U.S.C. 360), Food and Drugs, Drugs and Devices: Registration of Producers of Drugs or Devices, http://www.gpo.gov/fdsys/pkg/USCODE-2011-title21/pdf/USCODE-2011-title21-chap9-subchapV-partA-sec360.pdf.

Congressional Hearings

The House Energy and Commerce Committee and the Senate Committee on Health, Education, Labor, and Pensions held hearings on the 2012 fungal meningitis outbreak and its relationship to FDA authority to regulate compounded drugs and compounding pharmacies. These hearings and related documents are listed below.

- November 15, 2012, "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," hearing of the Senate Health, Education, Labor, and Pensions Committee, http://www.help.senate.gov/hearings/hearing/?id=5f5def0d-5056-a032-5297-eab57634d209.

  Materials available on the committee website include the hearing video, resources, and testimony.

  - United States Senate: Health, Education, Labor, and Pensions (HELP) Committee: Committee Staff Report, "The New England Compounding Center and the Meningitis Outbreak of 2012: A Failure to Address Risk to the Public Health," November, 15, 2012, http://www.help.senate.gov/imo/media/doc/11_15_12%20HELP%20Staff%20Report%20on%20Meningitis%20Outbreak.pdf.
  - Resources and source materials compiled by the committee staff: http://www.help.senate.gov/imo/media/doc/Attachments.pdf.

[24] For more information on legal issues, see CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

- Statement of Margaret Hamburg, Commissioner of Food and Drugs, at the Committee on Health, Education, Labor, and Pensions, U.S. Senate, November 15, 2012, http://www.help.senate.gov/imo/media/doc/Hamburg3.pdf.
- Other witness statements are available at http://www.help.senate.gov/hearings/hearing/?id=5f5def0d-5056-a032-5297-eab57634d209.

- November 14, 2012, "The Fungal Meningitis Outbreak: Could It Have Been Prevented?" hearing of the House Energy and Commerce Oversight and Investigations Subcommittee, http://energycommerce.house.gov/hearing/fungal-meningitis-outbreak-could-it-have-been-prevented.

  Materials available on the committee website include the complete hearing video, resources, opening statements, and testimony.

  - House Energy and Commerce Committee Majority Staff: Background Memorandum, November 14, 2012, http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/Hearings/OI/20121114/HMTG-112-HHRG-IF02-20121114-SD001.pdf.
  - Statement of Margaret Hamburg, Commissioner of Food and Drugs, at the Subcommittee on Oversight and Investigations, House Energy and Commerce Committee, November 14, 2012, http://www.fda.gov/NewsEvents/Testimony/ucm327664.htm.
  - The hearing transcript is available at http://www.cq.com/doc/congressionaltranscripts-4175157; http://www.cq.com/doc/congressionaltranscripts-4175202 (panel 2); and http://www.cq.com/doc/congressionaltranscripts-4175216 (panel 3).

- In past years, U.S. Senate committees have held hearings on different compounded drugs and compounding pharmacies.

  - April 19, 2007, "Bioidentical Hormones: Sound Science or Bad Medicine," S. Hrg. 110-129, Senate Special Committee on Aging, http://www.gpo.gov/fdsys/pkg/CHRG-110shrg37150/pdf/CHRG-110shrg37150.pdf.

    This hearing includes testimony by Jacques Rossouw, Chief of the Women's Health Initiative Branch, National Heart, Lung and Blood Institute, National Institutes of Health; Steven Galson, Director, Center for Drug Evaluation and Research, Food and Drug Administration; and Eileen Harrington, Deputy Director, Bureau of Consumer Protection, Federal Trade Commission.

  - October 23, 2003, "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients," S. Hrg. 108-378, Senate Committee on Health, Education, Labor, and Pensions, http://www.gpo.gov/fdsys/pkg/CHRG-108shrg90129/pdf/CHRG-108shrg90129.pdf.

    This hearing included testimony by Janet Heinrich, Director of Health Care—Public Health Issues, GAO, and Steven Galson, Deputy Director, Center for Drug Evaluation and Research, FDA.

Proposed Federal Legislation

This section includes selected proposed legislation on the federal regulation of compounded drugs and compounding pharmacies. To date, no legislation has been proposed in the 113th Congress. This section does not include bills that would expand payment or financing of certain compounded drugs for specific diseases or conditions.[25]

112th Congress

- **H.R. 6584**, Verifying Authority and Legality in Drug Compounding Act of 2012, Representative Markey.
- **H.R. 6638**, S.A.F.E Compounded Drug Act of 2012, Representative DeLauro.

110th Congress

- **H.Con.Res. 342**, Expressing the sense of Congress that the FDA's new policy restricting women's access to medications containing estriol does not serve the public interest, Representative Ross.
- A bipartisan group of members of the Senate Health, Education, Labor, and Pensions Committee created a discussion draft in 2007, which is listed below.
    - Senate Discussion Draft: "Safe Compounding Drug Act of 2007."[26]

  This draft elicited comments from a variety of interested parties, some of which are presented below.
    - American Pharmacists Association (APhA), letter from Executive Vice President John A. Gans to Senators Kennedy, Burr, and Roberts, "RE: Discussion Draft of 'Safe Drug Compounding Act of 2007,'" March 7, 2007, http://www.aphafoundation.org/AM/Template.cfm?Section=Home&ContentID=16068&template=/CM/ContentDisplay.cfm.
    - Larry D. Sasich, Consultant, Public Citizen's Health Research Group, "Comments on a Draft of the Safe Drug Compounding Act of 2007," March 5, 2007, http://www.citizen.org/publications/publicationredirect.cfm?ID=7519.
    - Consumers Union, "Groups support the intent of the Safe Drug Compounding Act of 2007," letter to Senate Committee on Health, Education, Labor, and Pensions from signed group of organizations, April 9, 2007, http://www.consumersunion.org/news/groups-support-the-intent-of-the-safe-drug-compounding-act-of-2007/.

[25] For example, see H.R. 232 in the 113th Congress; H.R. 6326, S. 3496 in the 112th Congress; and H.R. 1812 in the 110th Congress.

[26] Copies of this draft legislation are available from (name redacted), CRS, 7-.....

105th Congress

- **H.R. 1060**, Pharmacy Compounding Act, Representative Burr, March 21, 1997, http://www.congress.gov/cgi-lis/bdquery/z?d105:H.R.1060:/.
- **H.R. 1411**, Drug and Biological Products Modernization Act of 1997 (Introduced in House), Representative Burr.
- **H.R. 1411**, Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act (Reported in House), Representative Burr.

104th Congress

- **H.R. 598**, Pharmacy Compounding Preservation Act of 1994, Representative Brewster, January 20, 1995.
- **H.R. 3199**, Drug and Biological Products Reform Act of 1996, Representative Burr.

Other Congressional Documents

This section includes letters and reports from Members of Congress relevant to the 2012 fungal meningitis outbreak, compounded drugs, and compounding pharmacies.

- Senators Harkin and Enzi, U.S. Senate: Health, Education, Labor, and Pensions Committee, November 19, 2012, letter to state boards of pharmacy, http://www.help.senate.gov/newsroom/press/release/?id=3f3af08d-35ed-435c-abe0-86a53c84fb78&groups=Chair. This letter was sent to all state pharmacy boards requesting information on their states' regulation of compounding pharmacies.
- Senators Blumenthal, Stabenow, Franken, and Feinstein, November 15, 2012, letter to Marilyn Tavenner, Acting Director, Centers for Medicare and Medicaid Services (CMS), http://op.bna.com/hl.nsf/id/bdmr-927rru/$File/Blumenthalletter.pdf. This letter requests information on the coordination of information between the FDA and CMS regarding compounding drug violations and Medicaid and Medicare payment policies.
- Representatives Markey, Waxman, Dingell, Pallone, DeGette, and Eshoo, November 15, 2012, letter to Gene Dodaro, U.S. Comptroller General, Government Accountability Office (GAO), http://markey.house.gov/document/2012/letter-gao-group-purchasing-organization. This letter requests that GAO investigate whether contracting practices by Group Purchasing Organizations and others in the prescription drug supply chain have had effects on drug pricing, drug shortages, and demand for compounded drugs.
- Report of the Office of Representative Markey, "Compounding Pharmacies, Compounding Risk," October 29, 2012, http://markey.house.gov/document/2012/compounding-pharmacies-compounding-risk-report. This report explores issues in the current regulation of compounding pharmacies.

Congressional Support Agency Products

Congressional Research Service (CRS)

The following CRS materials address legal issues in drug compounding as well as federal regulation relevant to the current issues posed by the 2012 fungal meningitis outbreak.

- CRS Legal Sidebar, "Meningitis Outbreak Sheds Light on Regulation of Compounded Drugs," by Jennifer Staman, October 19, 2012, http://www.crs.gov/analysis/legalsidebar/pages/details.aspx?ProdId=276.
- CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman, October 17, 2012.

Government Accountability Office (GAO)

This testimony by Janet Heinrich, Director, Health Care—Public Health Issues, was delivered to the Committee on Health, Education, Labor, and Pensions of the U.S. Senate (October, 23, 2003).

- GAO, "Prescription Drugs: State and Federal Oversight of Drug Compounding by Pharmacies," GAO-04-195T, October 23, 2003, http://www.gao.gov/assets/120/110456.pdf.

FDA Agency Guidance and Regulations, Meetings, and Related Documents

Guidance and Regulations

Compliance Policy Guidance on Pharmacy Compounding CPG 460.200

The following FDA guidance addresses drug compounding.[27] FDA reissued this CPG after the appellate court decisions. (See "Federal Law.")

- FDA, "CPG Sec. 460.200, Pharmacy Compounding," Compliance Policy Guidance for FDA Staff and Industry, May 2002, http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm.

In this guidance, excerpted below, FDA identifies its authorities over certain types of activities of compounding pharmacies—those akin to manufacturers—while otherwise deferring to the regulatory prerogative of state pharmacy boards.[28]

[27] Please note, agency rules have the force and effect of law; guidance documents are considered to be a general statement of policy.

[28] For a discussion of the legal and regulatory issues in light of legal challenges, see S. A. Coffina, "Coming Soon: Increased Scrutiny of Compounding Pharmacies," Bloomberg/BNA Pharmaceutical Law & Industry Report (continued...)

> Generally, FDA will continue to defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. FDA anticipates that, in such cases, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions by the states.
>
> However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action.

Drugs Not to Be Compounded

This regulation lists drugs withdrawn or removed from the market for reasons of safety or effectiveness and which may not be compounded under the exemptions of Section 503A(a) of FFDCA.

- 21 CFR 216.24, Food and Drug Administration, Pharmacy Compounding, April 1, 2011, http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol4/pdf/CFR-2011-title21-vol4-part216.pdf.

FDA Meetings

On December 19, 2012, the FDA held two meetings regarding state and federal roles in pharmacy compounding. FDA first had an intergovernmental meeting with state officials and then hosted a public meeting titled "Framework for Pharmacy Compounding: State and Federal Roles." This public meeting included a summary of the results of the earlier intergovernmental meeting on the different roles of state and federal governments in regulating compounded drugs and compounding pharmacies. The meeting materials, archived webcast, and transcript are available on the FDA website:

- FDA, "Framework for Pharmacy Compounding: State and Federal Roles," www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm330617.htm.

Other FDA Documents

The following FDA documents address compounding activities.

- FDA, "The Special Risks of Pharmacy Compounding," posted May 31, 2007, page last updated August 9, 2012, http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm107839.pdf.
- FDA, "CPG Sec. 460.100, Hospital Pharmacies—Status as Drug Manufacturer," Compliance Policy Guide, issued October 1, 1980, page last updated January 20, 2010, http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074397.htm.

(...continued)

(November 16, 2012), and CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*, by Jennifer Staman.

The documents below discuss FDA requirements for prescription drug manufacturers, including those relating to adverse event reporting, inspections, sterility, and Current Good Manufacturing Practices (CGMPs). These materials provide background information on the regulation of manufacturing practices considered important in assuring the safety and effectiveness of prescription drugs.

- FDA, "MedWatch, The FDA Safety Information and Adverse Event Reporting Programs," http://www.fda.gov/Safety/MedWatch/default.htm.
- FDA, "Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations," page last updated September 7, 2012, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm.
- FDA, "Questions and Answers on Current Good Manufacturing Practice (CGMP) for Drugs," page last updated December 21, 2011, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm124740.htm.
- FDA, "Facts about Current Good Manufacturing Practices (CGMPs)," page last updated June 25, 2009, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm.
- FDA, "Dosage Form Drug Manufacturers cGMPs (10/93); Guide to Inspections of Dosage Form Drug Manufacturers—CGMPRS," Inspection Guides, page last updated April 30, 2009, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074927.htm.
- FDA, "Sterile Drug Substance Manufacturers (7/94); Guide to Inspections of Sterile Drug Substance Manufacturers," page last updated April 30, 2009, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074930.htm.
- FDA, "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice," Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), Pharmaceutical CGMPs, September 2004, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.

FDA Actions on Drug Compounding

Pharmacy Compounding

The FDA maintains a webpage with information on pharmacy compounding with a variety of information, including news and updates; information for consumers; information for health care providers; regulatory and policy information; FDA actions; and related topics.

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

Fungal Meningitis Outbreak

The FDA maintains a website with updates on the 2012 fungal meningitis outbreak.

- FDA, "Multistate outbreak of fungal meningitis and other infections," http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm.

Selected FDA information bulletins and updates on the 2012 fungal meningitis outbreak are listed below in descending chronological order:

- FDA, "Questions and Answers on Fungal Meningitis Outbreak," page updated periodically, http://www.fda.gov/Drugs/DrugSafety/ucm322735.htm.
- FDA, New England District Office to NECC Re: Inspections on October 1-2, 4-5, 9, 15, and 26, 2012, Form FDA 483 Inspectional Observations, Date Issued: October 26, 2012, http://insidehealthpolicy.com/iwpfile.html?file=oct2012%2Fhe10262012_necc.pdf.[29]
- FDA, "New England Compounding Center (NECC) Potentially Contaminated Medication: Fungal Meningitis Outbreak," MedWatch: The FDA Safety Information and Adverse Event Reporting Program, October 5, 2012, http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm322849.htm.
- "New England Compounding Center Issues Voluntary Nationwide Recall of All Products," Firm Press Release, October 6, 2012, posted at FDA, http://www.fda.gov/Safety/Recalls/ucm322901.htm.
- CDC, "CDC and FDA Joint Telebriefing on Investigation of Meningitis Outbreak," Press Briefing Transcript, October 4, 2012, http://www.cdc.gov/media/releases/2012/t1004_meningitis_outbreak.html.

The following is a selection of FDA announcements and actions relevant to different compounded products and the marketing of prescription drugs without required FDA approval. These documents were selected based on their relevance to policy issues in the federal oversight of compounded drugs.

- FDA, "FDA Reports Voluntary Recall of All Ameridose Drug Product," November 12, 2012, http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/ucm326384.htm.
- FDA, "Pharmacy Compounding," page last updated October 10, 2012, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.
- FDA, "Unapproved Drugs: Drugs Marketed in the United States That Do Not Have Required FDA Approval," page last updated August 22, 2012, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm.
- FDA, "Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena),"[30] Press

[29] For the full text of articles, please contact (name redacted), CRS, 7-.....

[30] This prescription drug is used to reduce the risk of preterm birth.

Announcements, June 15, 2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm.

- FDA, "FDA Statement on Makena," Press Announcements, November 8, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279098.htm.
- FDA, "Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide; Sec. 440.100. Marketed New Drugs Without Approved NDAs or ANDAs," September, 19, 2011, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf.
- FDA, "FDA Alerts Health Care Professionals of Infection Risk from Repackaged Elastin Intravitreal Injections," page last updated August 30, 2011, http://www.fda.gov/Drugs/DrugSafety/ucm270296.htm.
- FDA, "FDA Statement on Makena," Press Announcements, March 30, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm.
- FDA, "News for Pharmacy Compounders in Regards to Possible Melamine Contamination of Pharmaceutical Components," page last updated 09/23/2009, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183052.htm.
- FDA, "Questions and Answers about FDA's Enforcement Action against Unapproved Injectable Colchicine Products," page last updated May 15, 2009, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119642.htm.
- FDA, "FDA Takes Action Against Compounded Menopause Hormone Therapy Drugs," FDA News Release, January 9, 2008, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm.
- FDA, "Warning Letter," to New England Compounding Center, December 4, 2006, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076196.htm.

Other Federal Agency Actions and Resources

Centers for Disease Control and Prevention (CDC)

CDC is involved in the 2012 fungal meningitis outbreak due to its responsibility to protect public health, including through disease surveillance. CDC has taken specific actions related to the 2012 fungal meningitis outbreak. The following is a selection of CDC announcements and actions chosen based on their relevance to policy issues in the federal oversight of compounded drugs.

- CDC, "Multistate Fungal Meningitis Outbreak Investigation," http://www.cdc.gov/hai/outbreaks/meningitis.html.

Selected CDC information bulletins and updates, and *Morbidity and Mortality Weekly Reports (MMWR)*, are listed below.

- CDC, "Current Case Count," http://www.cdc.gov/hai/outbreaks/meningitis-map.html.
- "Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy—United States, 2012," *MMWR*, October 19, 2012, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6141a4.htm.
- CDC, "CDC and FDA Joint Telebriefing on Investigation of Meningitis Outbreak," Press Briefing Transcript, October 4, 2012, http://www.cdc.gov/media/releases/2012/t1004_meningitis_outbreak.html.
- CDC, "Meningitis and Stroke Associated with Potentially Contaminated Product," CDC Health Advisory, October 4, 2012, http://emergency.cdc.gov/HAN/han00327.asp.
- "Notes from the Field: Multistate Outbreak of Postprocedural Fungal Endophthalmitis Associated with a Single Compounding Pharmacy—United States, March-April 2012," *MMWR*, vol. 61, no. 17 (May 4, 2012), pp. 30-31, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6117a5.htm.

Department of Justice (DOJ)

DOJ is involved in drug compounding issues through its responsibility to enforce the federal laws of the United States, including those regulating prescription drugs, compounded drugs, and compounding pharmacies. DOJ has pursued legal action in the past related to pharmacies that compound drugs; the following list represents cases found on the DOJ website.

- U. S. Department of Justice (DOJ), "Dallas Compounding Pharmacy Owner Pleads Guilty in Connection with Misbranded Drug Shipment," press release, April 24, 2012, http://www.justice.gov/opa/pr/2012/April/12-civ-526.html. The press release stated that the pharmacist and the corporation pleaded guilty to misdemeanor violations of FFDCA by sending sub and super potent drugs across state lines. The press release also stated that three patients died as a result.
- DOJ, "U.S. Seeks Permanent Injunction Against Florida-Based Drug Compounding Lab," press release, April 9, 2010, http://www.justice.gov/opa/pr/2010/April/10-civ-438.html. The press release stated that a civil suit was filed alleging that the pharmacy had been introducing adulterated, misbranded, and unsafe drugs into interstate commerce.
- DOJ, Drug Enforcement Administration, "Docket No. 04-8, Wedgewood Village Pharmacy; Revocation of Registration," Federal Register Doc. E6-4771, April 3, 2006, http://www.deadiversion.usdoj.gov/fed_regs/actions/2006/fr0403.htm. This case involved the FDA's authority to inspect compounding pharmacies whose activities are more akin to those of manufacturers. This case was resolved by the Third Circuit Court of Appeals in 2005.

Selected State Resources

Massachusetts

The Board of Registration in Pharmacy of the Massachusetts Executive Office of Health and Human Services (EOHHS) licenses pharmacy professionals and pharmacies. The EOHHS maintains a website specific to the 2012 fungal meningitis outbreak and the New England Compounding Center (NECC) product recall and investigation.

- Massachusetts EOHHS, "NECC Product Recall and Investigation," http://www.mass.gov/eohhs/provider/licensing/occupational/pharmacy/.
- Massachusetts EOHHS, "Patrick-Murray Administration Appoints Chair of Special Commission on Compounding Pharmacies; Emergency Regulations Passed to Enhance Oversight of Industry," Press Release, November 1, 2012, http://www.mass.gov/eohhs/gov/newsroom/press-releases/dph/chair-of-special-commission-on-compounding-pharmacies.html.
- Massachusetts EOHHS, "Pharmacy Board Draft Emergency Regulations," November 1, 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/121101-pharmacy-board-draft-emergency-regs.pdf.
- Massachusetts EOHHS, "New England Compounding Center (NECC): Preliminary Investigation Findings," Board of Registration in Pharmacy Report, October 23, 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/necc-preliminary-report-10-23-2012.pdf.
- Massachusetts EOHHS, "Statement of Dr. Madeleine Biondolillo," Director of the [Massachusetts] Bureau for Health Care Safety and Quality, Joint DPH / FDA / CDC Teleconference Call, October 11, 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy-121011-statement-madeleine-biondolillo.pdf.
- Massachusetts EOHHS, "Alert—New England Compounding Center Product Recall Information," Press Release, October 4, 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy-alert-necc.pdf.

Colorado

Colorado took actions against NECC in 2011 and 2012 for the unlawful distribution of prescription drugs. The documents below are related to those actions.

- Colorado State Board of Pharmacy, "Special Report: New England Compounding Pharmacy, Inc. (WHO 7832)," July 20, 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy/120720-colorado-state-board-of-pharmacy-report.pdf.
- E-mail correspondence between Colorado State Board of Pharmacy and Massachusetts Board of Registration of Pharmacy regarding NECC, July 2012, http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy/120727-colorado-state-board-of-pharmacy-email.pdf.

Tennessee

Tennessee was one of the first states to identify the 2012 fungal meningitis outbreak. Its Department of Health maintains a website focusing on the 2012 fungal meningitis outbreak.

- Tennessee Department of Health, "Multistate Meningitis Outbreak Investigation," http://health.state.tn.us/outbreakinvestigation.shtml.

Articles from Legal, Professional, and Scientific Journals[31]

This section lists selected articles selected from a search of PubMed/Medline. The search terms focus on public health concerns and included variations of pharmacy compounding, compounded drugs, adverse effects, and fatalities.

Selected 2013 Articles on Compounded Drugs

- Beth. P. Bell and Rima F. Khabbaz, "Responding to the Outbreak of Invasive Fungal Infections: The Value of Public Health to Americans," *JAMA, The Journal of the American Medical Association*, vol. 309, no. 9, March 6, 2013, pp. 883-884, http://jama.jamanetwork.com/article.aspx?articleid=1567243.
- Joseph V. Pergolizzi Jr, Sumedha Labhsetwar, and Jo AnnLeQuang, "Compounding Pharmacies: Who is in Charge?," *Pain Practice*, vol. 13, no. 3, pp. 253-257, March, 2013; January 28, 2013, on-line, http://onlinelibrary.wiley.com/doi/10.1111/papr.12033/abstract.
- Roy Guharoy et al., "Compounding Pharmacy Conundrum: 'We Cannot Live Without Them But We Cannot Live With Them' According to the Present Paradigm," CHEST, February 14, 2013, http://journal.publications.chestnet.org/article.aspx?articleID=1570173 (abstract).

Selected Articles on the 2012 Fungal Meningitis Outbreak and Compounding Pharmacies

- Jeffrey M. Drazen, Gregory D. Curfman, Lindsey R. Baden, and Stephen Morrissey, "Editorial: Compounding Errors," *New England Journal of Medicine*, November 8, 2012, http://www.nejm.org/doi/full/10.1056/NEJMe1213569.
- Kevin Outterson, "Perspective: Regulating Compounding Pharmacies after NECC," *New England Journal of Medicine*, November 7, 2012, http://www.nejm.org/doi/full/10.1056/NEJMp1212667.
- Marion A. Kainer et al., "Fungal Infections Associated with Contaminated Methylprednisolone in Tennessee," *New England Journal of Medicine*, November 6, 2012, http://www.nejm.org/doi/pdf/10.1056/NEJMoa1212972.

[31] For the full text of articles, please contact (name redacted), CRS, 7-.....

- Lucy E. Wilson et al., "Fungal Meningitis from Injection of Contaminated Steroids," *New England Journal of Medicine,* October 26, 2012, http://jama.jamanetwork.com/article.aspx?articleid=1387597.
- W.J. Zohler, "Steps to Improve Quality in the Compounding Lab," *International Journal of Pharmaceutical Compounding*, vol. 16, no. 2, March-April, 2012, pp. 136-144, http://www.ncbi.nlm.nih.gov/pubmed/23050326 (abstract).

Selected Articles Regarding Safety Issues and Compounding Pharmacies 2006 on

- S. Huang, et al., Notes from the field: Multistate outbreak of post procedural fungal endophthalmitis associated with a single compounding pharmacy, Morbidity and Mortality Weekly Report (MMWR), vol. 61, no. 17, March-April 2012, pp. 310-311, http://www.medscape.com/viewarticle/763654.
- Robert A. Goldberg et al., "An Outbreak of Streptococcus Endophthalmitis After Intravitreal Injection of Bevacizumab," *American Journal of Ophthalmology*, February 2012, pp. 204-208.
- Cheryl A. Thompson, "Bacteremia Outbreak Tied to Improper Filtration by Compounding Pharmacy," *American Journal of Health-System Pharmacy*, vol. 68, no. 21, November 15, 2011, pp. 2110-12.
- Neil Gupta et al., "Investigation of an outbreak of *Serratia marcescens* Bloodstream infections in patients receiving total parenteral nutrition—Alabama, 2011." Authors affiliated with CDC and Alabama Dept. of Health, Paper presented at conference IDSA, October, 2011, https://idsa.confex.com/idsa/2011/webprogram/Paper31248.html.
- Helen M. Steel et al., "Fatal Respiratory Events Caused by Zanamivir Nebulization," *Clinical Infectious Diseases*, vol. 51, no. 1, July 1, 2010, p. 121, http://cid.oxfordjournals.org/content/51/1/121.1.full.pdf+html.
- Lisa A. Maragakis et al., "*Sphingomonas paucimobilis* Bloodstream infections associated with contaminated intravenous fentanyl," *Emerging Infectious Disease*, vol. 15, no. 1, 2009, pp. 12-18.
- Tamira Mullarkey, "Pharmacy compounding of high-risk level products and patient safety," *American Journal of Health-System Pharmacy*, vol. 66, no. 17, supp. 5, September 1, 2009, pp. S4-S13 [PDF pp. 5-14], http://www.ashp.org/DocLibrary/CE/09004AJHP_suppl5_2009.pdf.
- Larry D. Sasich, "Unknown Risks of Pharmacy—Compounded Drugs," *Journal of the American Osteopathic Association*, vol. 108, no. 2, February 1, 2008, pp. 51-52.
- Bruce Patsner, "Pharmacy Compounding of Bioidentical Hormone Replacement Therapy (BHRT): A Proposed New Approach to Justify FDA Regulation of These Prescription Drugs," *Food and Drug Law Journal*, 2008 (63 Food Drug L.J. 459).
- Daniel Meron, "Legal Developments Relevant to FDA Authority," *Food and Drug Law Journal*, 2007 (67 Food Drug L.J. 441).

- Karen S. McCoy, "Compounded Colistimethate as Possible Cause of Fatal Acute Respiratory Distress," *New England Journal of Medicine*, vol. 357, November 29, 2007, pp. 2310-2311, http://www.nejm.org/doi/full/10.1056/NEJMc071717.
- N. J. McKeown et al., Deaths from intravenous colchicine resulting from a compounding pharmacy error—Oregon and Washington, 2007, October 12, 2007, 56(40) 1050-1052, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5640a3.htm.
- Rebecca H. Sunenshine et al., "A Multi-state Outbreak of *Serratia marcescens* Bloodstream Infection Associated with Contaminated Intravenous Magnesium Sulfate from a Compounding Pharmacy," *Clinical Infectious Diseases*, vol. 45, no. 5, September 1, 2007, pp. 527-533, http://cid.oxfordjournals.org/content/45/5/527.full.pdf+html.
- Rachel Civen et al., "Outbreak of *Serratia marecescens* Infections Following Injection of Betamethasone Compounded at a Community Pharmacy," *Clinical Infectious Diseases,* vol. 43, no. 7, August 22, 2006, pp. 831-837, http://cid.oxfordjournals.org/content/43/7/831.full.pdf+html.
- Melissa R. Held et al., "Life-Threatening Sepsis Caused by *Burkholderia cepacia* From Contaminated Intravenous Flush Solutions Prepared by a Compounding Pharmacy in Another State," *Pediatrics*, June 19, 2006, http://pediatrics.aappublications.org/content/118/1/e212.full.pdf+html.

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