

Description of outbreaks of health-care-associated infections related to compounding pharmacies, 2000–12

CATHERINE STAES, JASON JACOBS, JEANMARIE MAYER, AND JILL ALLEN

The 2012 multistate fungal meningitis outbreak caused by contaminated injectable methylprednisolone manufactured by New England Compounding Center (NECC) has raised concerns about the quality of compounded drugs.¹ Within two months of initially detecting the outbreak, the Centers for Disease Control and Prevention (CDC) and state health agencies identified 490 patients with serious fungal infection, including meningitis, stroke, other infection related to the central nervous system ($n = 478$), and joint infection ($n = 12$); 34 patients had died, and the outbreak involved 19 states.² CDC estimated that approximately 14,000 patients received injections from three lots of methylprednisolone.² The number of patients exposed to this contaminated compounded drug is unprecedented, the clinical consequences are severe, and many of the affected patients who survived will undergo additional invasive procedures and treatments.³ This scenario is un-

Purpose. Outbreaks of health-care-associated infections related to compounding pharmacies from 2000 through 2012 are described.

Methods. PubMed and the websites for the Centers for Disease Control and Prevention and the Food and Drug Administration were searched to identify infectious outbreaks associated with compounding pharmacies outside the hospital setting between January 2000 and November 2012.

Results. Between January 2000 and before the 2012 fungal meningitis outbreak, 11 outbreaks were identified, involving 207 infected patients and 17 deaths after exposure to contaminated compounded drugs. The 2012 meningitis outbreak had a similar mortality rate but increased these totals almost fivefold. Half of the outbreaks involved patients in more than one state. Three outbreaks involved ophthalmic drugs. The remaining outbreaks involved corticosteroids, heparin flush solutions, cardioplegia solution, i.v. magnesium sulfate, total parenteral

nutrition, and fentanyl. The outbreaks were caused by pathogens commonly associated with health-care-associated infections, common skin commensals, and organisms that rarely cause infection. Morbidity was substantial, including vision loss. Half the outbreaks resulted in recall of all sterile drugs from the pharmacy due to systemic problems with sterile procedures.

Conclusion. Before the nationwide 2012 fungal meningitis outbreak, drugs produced by compounding pharmacies were associated with 11 other smaller, but equally serious, outbreaks that occurred sporadically over the past 12 years. Lapses in sterile compounding procedures led to contamination of compounded drugs, exposure to patients, and a threat to public health in these outbreaks. Recognition and subsequent public health investigation were usually triggered by the occurrence of illness among multiple patients in a single health care setting.

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usual but may only be the tip of the iceberg.

Under the traditional definition of pharmacy compounding, a phar-

macist compounds a medication for a single patient after receiving a prescription written by a single clinician.⁴ Traditional compound-

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ing practices are regulated by state boards of pharmacy to meet the needs of patients not served by medications with Food and Drug Administration (FDA)-approved labeling. Compounding pharmacies are not required to establish efficacy and safety, obtain FDA approval, or comply with manufacturing and labeling standards for compounded drugs.⁵ In contrast, drug manufacturers are regulated by FDA and must comply with good manufacturing practices. Over the past few decades, the regulatory gap between state regulation of traditional compounding practices and FDA regulation of drug manufacturing has allowed the proliferation of compounding pharmacies that distribute large quantities of compounded sterile products nationwide. According to the International Academy of Compounding Pharmacists, 1–3% of all prescriptions in the United States are compounded.⁶ An estimated 7500 pharmacies in the United States provide advanced compounding services, 3000 of which provide sterile compounding services.⁶ Only about 2% of compounding pharmacies participate in the industry's voluntary accreditation program.⁵

Since 2000, FDA has issued numerous warnings about the quality of compounded drugs,¹ including problems with potency^{7–10} and sterility¹¹ and the presence of particulates^{12,13} or contaminants.^{14,15} In 2001 and 2006, FDA investigators found that 30% of the compounded drug samples they tested contained either too little or too much of the active ingredient,^{16,17} compared with less than 2% of FDA-approved prescription drugs.¹⁶

In the past, potential outbreaks have been averted before compounded drugs reached large numbers of patients.¹⁸ In 2003, a compounding pharmacy that specialized in respiratory drugs issued a partial recall of two batches of albuterol–ipratropium respiratory solution (more than 1

million doses) that were contaminated with *Burkholderia cepacia*.¹¹ A full recall was issued after the Missouri Board of Pharmacy obtained a restraining order to halt further dispensing of contaminated respiratory solutions. More than 19,000 patients throughout the United States may have been exposed to the contaminated drug, but no known infections resulted from this event.

We questioned whether infectious outbreaks associated with contaminated compounded drugs are a new or recurring problem and whether there are features associated with compounded drugs or surveillance systems that may hinder outbreak detection. Outbreak detection requires that a person or automated system recognizes unusual events and that systems are in place to enable reporting and investigation. Therefore, the objectives of this analysis were to describe features of infectious outbreaks associated with exposure to contaminated drugs produced by compounding pharmacies outside the hospital setting, sterile compounding procedures associated with microbial contamination, and outbreak features relevant for detection and investigation.

Methods

A literature search was conducted in PubMed using the MeSH term combinations *drug compounding* and *drug contamination*, *drug compounding* and *disease outbreaks*, *drug compounding* and *medication errors*, *drug compounding* tagged with the subheading *adverse effects*, and drug contamination with the search term for publications in *Morbidity and Mortality Weekly Report (MMWR [ta])*. A total of 850 citations, published between January 2000 and November 2012, were returned and reviewed. The content on FDA's Pharmacy Compounding webpage¹ was manually reviewed to identify the name of potential pharmacies involved in outbreaks, followed by

a search of FDA's website for additional documents related to the pharmacies identified. Terms associated with compounding pharmacies and the infectious organisms in the identified outbreaks were used to manually search the *Morbidity and Mortality Weekly Report (MMWR)*¹⁹ and abstracts from the Epidemic Intelligence Service (EIS) annual meetings from 2006 through 2012.²⁰ This additional search was necessary to query for additional outbreaks and to obtain additional information about previously identified outbreaks.

The analysis focused on infectious outbreaks in the United States that resulted from exposure to drugs that were likely contaminated during production by a compounding pharmacy and was limited to compounding pharmacies that prepared sterile products outside the hospital setting.

After identifying an outbreak that met the selection criteria, information (in order of precedence if content differed between sources) from government publications (including FDA Enforcement Letters and recall notices), peer-reviewed literature, congressional testimony, and meeting abstracts was extracted. The information was used to describe the (1) triggers that led to outbreak detection, (2) number and location of patients involved, (3) drug name and route of administration, (4) infectious organisms and clinical outcomes, (5) name and location of the compounding pharmacy, and (6) findings from the investigation. For one outbreak, the publication indicated that patients were located in seven states but the states were not identified. We assumed that the seven state public health officials that authored the report represented the states where patients were identified.²¹

Results

A total of 12 outbreaks—including the most recent outbreak associated with NECC—met the inclusion criteria (Table 1).^{22–56}

These outbreaks specifically involved pharmacies that compound drugs outside of the hospital setting. No single source provided information about all 12 outbreaks. Ten of the eligible outbreaks were identified using PubMed (6 were reported in peer-reviewed journals, 2 in *MMWR*, and 2 in both *MMWR* and a peer-reviewed journal). Two additional outbreaks were identified from EIS meeting abstracts (outbreaks 7 and 9). Information about five of the pharmacies involved in the identified outbreaks were listed on the FDA Pharmacy Compounding webpage as of November 28, 2012 (outbreaks 4, 7, and 9–11). Information about outbreak 12, the NECC multistate fungal meningitis outbreak, was readily available on the FDA site. Once we identified the names of pharmacies involved, we found additional documents about 9 of the outbreaks using the FDA website search engine (outbreaks 2, 4–7, and 9–12). The outbreaks identified were investigated by state or federal public health authorities or both.

Outbreak descriptions. Between January 2000 and before the 2012 fungal meningitis outbreak associated with NECC, 11 outbreaks were identified, involving 207 infected patients and 17 deaths after exposure to contaminated compounded drugs (Table 1). The overall case fatality rate was 8.2%. When the 2012 fungal meningitis outbreak was included, the totals increased almost fivefold (as of March 9, 2013), to 927 infected patients with 65 deaths (case fatality rate: 7%).

Including the 2012 fungal meningitis outbreak, the 12 outbreaks were associated with 13 drugs (Table 1). Three outbreaks involved four ophthalmic drugs: trypan blue ophthalmic solution used during cataract surgery, brilliant blue-G ophthalmic solution used during vitrectomy, and triamcinolone and bevacizumab for intravitreal injection. Three out-

breaks involved methylprednisolone or betamethasone primarily for epidural injections. Two outbreaks involved heparin flush and heparin–vancomycin flush solutions for indwelling catheters. The remaining 4 outbreaks involved cardioplegia solution and i.v. magnesium sulfate, total parenteral nutrition, and fentanyl.

The most recent 3 outbreaks involved drugs that were preservative-free formulations intended for intravitreal, intraarticular, or epidural injection. Information about preservatives was not available for earlier outbreaks.

The outbreaks were caused by organisms commonly implicated in health care-associated infections (*Serratia marcescens* [3 outbreaks], *B. cepacia* [2 outbreaks], and *Pseudomonas aeruginosa* [1 outbreak]), organisms considered commensal but that can be associated with infection (*Streptococcus mitis* and *Streptococcus oralis* [1 outbreak]), and organisms that rarely cause infection (*Exserohilum rostratum*, *Fusarium incarnatum-equiseti*, *Bipolaris hawaiiensis*, *Pseudomonas fluorescens*, *Exophiala dermatitidis*, and *Sphingomonas paucimobilis*). The time between exposure and onset or recognition of symptoms varied among the outbreaks by organism, route of exposure, and presence of indwelling catheters (Table 1). For example, in the outbreak of bloodstream infections caused by *P. fluorescens*, 59% of the 80 patients developed symptoms within 24 hours after exposure to contaminated heparinized 0.9% sodium chloride injection flush solution, while the remaining 41% were diagnosed 84–421 days after the last potential exposure to a contaminated flush.³⁰ Delayed onset of symptoms and recognition of infection were also observed in the 2012 fungal meningitis outbreak.⁵⁷

Among the 65 patients who died in all 12 outbreaks (as of March 9, 2013), at least 38 died of meningitis (and 14 others died from menin-

gitis or other causes⁵¹) after epidural injections of betamethasone or methylprednisolone, 10 died of bloodstream infections after i.v. administration of magnesium sulfate or total parenteral nutrition, and 3 died of systemic inflammatory response syndrome after the administration of a cardioplegia solution during coronary artery bypass-graft surgery. The case-fatality rate varied by route of administration, ranging from 27% for patients who received contaminated cardioplegia solution during heart surgery, to 7.8% for drugs administered intravenously, to 7.0% for epidurally or intraarticularly administered drugs.

Of the 51 case-patients who developed endophthalmitis after exposure to contaminated trypan blue or brilliant blue G during ophthalmic surgery or intravitreal injection of bevacizumab or triamcinolone, none died. However, 80–83% of patients with endophthalmitis required repeat surgery (in outbreaks 10 and 11) or experienced high rates of vision loss (77–100% in the three outbreaks), and 5 patients (10%) underwent evisceration or enucleation of the affected eye.^{21,35,44}

Implicated pharmacies and practices. Drugs involved in the outbreaks were compounded by 12 pharmacies located in 10 states throughout the United States (Table 1). Two thirds ($n = 8$) of the outbreaks involved patients exposed to drugs compounded by a pharmacy located in a different state other than the patient's residence or location of care (Figure 1), and half involved patients identified in multiple states. In only 3 outbreaks, the compounding pharmacy and patients were located in the same state. One additional outbreak (outbreak 6) was likely limited to one state, but the location of the patients was not provided.³⁵

A source of contamination at the implicated pharmacy was not established in 5 outbreaks. However, the remaining investigations uncovered

Table 1.
Summary of Outbreaks Associated With Contaminated Drugs Produced by Compounding Pharmacies Outside of the Hospital Setting, January 2000–November 2012

| Outbreak No. (Yr) | Pharmacy Name and Location | Drug (Route) ^a | Initial Presentation of Outbreak and Infectious Organism | Morbidity and Mortality |
|---------------------------|---|--|--|---|
| 1 ^{22,23} (2001) | Doc's Pharmacy, Walnut Grove, CA | Betamethasone (epidural, conjunctival, ^b or intraarticular injection) | 4 pts at 1 hospital; <i>Serratia marcescens</i> (incubation period: 6 hr–15 days) | Total no. cases, 11; meningitis (<i>n</i> = 5, 3 deaths); epidural abscess (<i>n</i> = 5); septic arthritis (<i>n</i> = 1) |
| 2 ²⁴⁻²⁶ (2002) | Urgent Care Pharmacy, Spartanburg, SC | Methylprednisolone suspension (epidural injection) | 2 pt specimens at 1 laboratory noted by mycology staff (1 pt hospitalized elsewhere); <i>Exophiala dermatitidis</i> (incubation period: 34–152 days) | Total no. cases, 6; meningitis (<i>n</i> = 4, 1 death); septic arthritis (<i>n</i> = 2) |
| 3 ²⁷ (2004) | Pharmacy name unknown, FL | Heparin–vancomycin flush solution (i.v.) | 2 pediatric pts treated by same physician within 1 wk; <i>Burkholderia cepacia</i> (incubation period: ~1 hr) | Total no. cases, 2; sepsis (with seizure activity) in both pts |
| 4 ^{28,29} (2005) | PharMEDium Services LLC, Houston, TX | Magnesium sulfate (i.v.) | 6 pts in cardiac surgery unit noted by infection-control department at 1 hospital; <i>S. marcescens</i> (incubation period: <24–72 hr) | Total no. cases, 19 (1 death) ^d ; bloodstream infections |
| 5 ³⁰⁻³⁴ (2005) | IV Flush, Rowlett, TX | Heparinized 0.9% sodium chloride flush solution (i.v.) | 4 pts at 1 oncology clinic; <i>Pseudomonas fluorescens</i> (incubation period: early onset, 8 hr; delayed onset, 84–421 days) | Total no. cases, 80 (no deaths); bloodstream infections |
| 6 ^{35,36} (2005) | Custom RX Compounding Pharmacy, Richfield, MN | Trypan blue 0.06% solution (ophthalmic) | 2 pts after cataract surgery on same day at 1 hospital; <i>Pseudomonas aeruginosa</i> or <i>Burkholderia cepacia</i> (incubation period: 1–94 days) | Total no. cases, 6 (no deaths); endophthalmitis (permanent vision loss; 2 pts underwent enucleation of affected eye) |
| 7 ³⁷⁻⁴⁰ (2005) | Central Admixture Pharmacy Services, Inc., Lanham, MD | Cardioplegia solution (cardiac perfusion) | 3 pts over 8 days after cardiac bypass surgery at 1 hospital; multiple gram-negative bacilli and endotoxin (incubation period: <24 hr) | Total no. cases, 11 (3 deaths); systemic inflammatory response syndrome |
| 8 ^{41,e} (2007) | Pharmacy name unknown, IL | Fentanyl 10 µg/mL in 250 mL 0.9% sodium chloride (i.v. injection) | 6 pt specimens over 2 wk noted by 1 hospital laboratory; <i>Sphingomonas paucimobilis</i> (incubation period: 48 hr) | Total no. cases, 8 (no deaths); bloodstream infections |
| 9 ^{42,43} (2011) | Meds IV Pharmacy, Birmingham, AL | Total parenteral nutrition (i.v.) | 5 pts at 1 hospital; <i>S. marcescens</i> (incubation period not reported) | Total no. cases, 19 (9 deaths); bloodstream infections |

| Contributing Factors | Lot(s) Involved and Scope of Product Recall |
|---|--|
| Pharmacy technician omitted final autoclaving step for single lot on single day; California Board of Pharmacy found improper segregation of sterile compounding area, inadequate staff training and supervision, and poor labeling practices; <i>S. marcescens</i> cultured on compounding equipment ^c | 1 lot of 60 vials (5 mL per vial) recalled; 35 of 51 recovered vials grew <i>S. marcescens</i> ; California forced recall of all ophthalmic and injectable drugs made by pharmacy |
| South Carolina Board of Pharmacy found improper autoclave performance, no sterility testing, and inadequate cleanroom practices | Estimated 1,000 vials dispensed from Feb to Jul 2002; <i>E. dermatitidis</i> cultured from unopened vials in 3 lots; all injectable products from company recalled because sterility could not be ensured |
| Source of <i>B. cepacia</i> contamination in pharmacy not identified; FDA inspection did not identify specific deficiencies ^c | 1 lot of ~35 flush solutions made specifically for 2 pts; <i>B. cepacia</i> cultured in 1 of 21 flushes for pt 1 and 1 of 14 flushes for pt 2 |
| Definitive source of contamination not found, but manipulation of small admixture bags by compounding pharmacist was suspected source; samples from each lot were not retained or tested for sterility; FDA inspection of facilities in several states found problems with environmental monitoring, product labeling, and quality-assurance processes | 240 units per lot (50-mL admixtures); <i>S. marcescens</i> cultured from 3 of 20 units from lot A, which was shipped to 5 hospitals in 5 states. Patients in California received drug from another lot, but no samples available for testing. After multiple gram-negative organisms cultured from units in an additional lot, company recalled all magnesium sulfate lots and stopped making the product. |
| IV Flush contracted with a compounding pharmacy to make concentrated heparin solution that IV Flush then diluted and repackaged into syringes; Centers for Disease Control and Prevention (CDC) determined contamination occurred at IV Flush; sterility testing not performed for concentrated heparin solution or finished product; contamination of raw material unlikely; FDA inspection found global quality-assurance and production problems | No. doses and lots unclear; 7 of 9 lots of unopened prefilled syringes grew <i>P. fluorescens</i> ; product distributed to facilities in up to 17 states in year before outbreak detection; nationwide class I recall of product |
| Source of contamination in compounding pharmacy not identified. Details of FDA investigation could not be located. | 2 lots of 50 syringes each; <i>P. aeruginosa</i> cultured from 12 syringes and <i>B. cepacia</i> from 4 syringes in the lots; recall involved 5 lots |
| Compounding pharmacy was only likely source of contamination; FDA inspection at 4 facilities found multiple deficiencies including inadequate environmental monitoring, training of personnel, and quality-assurance processes and failure to maintain equipment | Gram-negative bacilli and endotoxin found in 2 lots of cardioplegia solution; outbreak led to recall of all of the company's injectable products |
| Evidence strongly suggested compounding pharmacy was source of outbreak ^c | 16 of 26 unopened i.v. bags from implicated lot grew <i>S. paucimobilis</i> ; 9 samples from 3 other lots produced no growth; no product recalled |
| Alabama Department of Public Health found deficiencies in mixing, filtration, and sterility testing; <i>S. marcescens</i> contamination likely from water faucet used to clean container in which total parenteral nutrition was mixed | No. doses and lots unknown; company recalled all i.v. compounded products |

Continued on next page

Table 1 (continued)

| Outbreak No. (Yr) | Pharmacy Name and Location | Drug (Route) ^a | Initial Presentation of Outbreak and Infectious Organism | Morbidity and Mortality |
|-------------------------------|---|---|---|---|
| 10 ⁴⁴⁻⁴⁸ (2011) | Infupharma, Hollywood, FL | Bevacizumab, preservative free (intravitreal injection) | 9 pts at 1 emergency department plus 3 consultations over 3 days; pts injected at 4 clinics; <i>Streptococcus mitis</i> and <i>Streptococcus oralis</i> (incubation period: 1–6 days) | Total no. cases, 12 (no deaths); endophthalmitis (permanent vision loss; 7 pts had globe loss) |
| 11 ^{21,49,50} (2012) | Franck's Compounding Laboratory, Ocala, FL | Brilliant blue-G, preservative-free, and triamcinolone, preservative-free (intravitreal injection) | 9 pts at 1 outpatient surgery center reported to public health department; <i>Fusarium incarnatum-equiseti</i> (brilliant blue-G) and <i>Bipolaris hawaiiensis</i> (triamcinolone) (incubation period not reported) | Total no. cases, 33; 3 underwent enucleation or evisceration endophthalmitis (vision loss, repeat ophthalmic surgery) |
| 12 ^{25,51-56} (2012) | New England Compounding Center (NECC), Framingham, MA | Methylprednisolone acetate suspension (80 mg/mL), preservative free (epidural or intra-articular injection) | 1 immunocompetent pt at an outpatient surgery center reported to Tennessee Department of Health by a physician; fungi (<i>Aspergillus</i> species and <i>Exserohilum</i> species) (incubation period: 1–4 wk, maximum not yet established) | Total no. cases, 720 (48 deaths ^f); meningitis, basilar stroke, spinal osteomyelitis or epidural abscess, septic arthritis or osteomyelitis of peripheral joint |

^aThe presence of preservatives in the drug was not indicated in the literature for the first nine outbreaks. FDA = Food and Drug Administration.

^bPatients with ophthalmic conditions who received drug by the conjunctival route did not get infected; these patients also received gentamicin prophylaxis.

^cInformation about outbreak was not found on FDA website.

^dEighteen case-patients were identified in the cluster reported by Susenshine et al.^{28,29} In the FDA investigation report, an additional patient died and was reported in another state.³¹

^eL. Maragakis, e-mail communication, 2012 Dec 15.

^fOn November 19, 2012, 34 deaths due to meningitis were reported by CDC. Subsequently, the CDC website reports deaths from all causes among persons who meet the case definition and may not be directly attributed to a fungal infection⁵¹; total number of cases and deaths reported as of March 9, 2013.

a myriad of problems, including improper autoclave performance or failure to follow autoclave procedures, no sterility testing of the finished product, inadequate clean-room or environmental sampling practices, failure to follow recommended filter-sterilization processes, and inadequate staff training and quality-assurance processes. After investigation, sterility could not be ensured for any products from the compounding facilities associated with 6 (50%) of the 12 outbreaks, leading to a recall of all of the companies' sterile products (outbreaks 1, 2, 7, 9, 11, and 12).

Outbreak detection. Scenarios that led to the initial recognition of

these outbreaks varied (Table 1). In 2 outbreaks (outbreaks 2 and 12), an astute clinician or laboratory worker reported one or two cases of rare infections that triggered active surveillance and a public health response. The remaining outbreaks were identified only when a cluster of patients from a common hospital or clinic presented with similar clinical characteristics to a common setting. The 2005 outbreak of *S. marcescens* bloodstream infections was independently detected in two states simultaneously. Investigation of the 2012 outbreak of fungal endophthalmitis associated with brilliant blue G led to the detection of a second contaminated drug (intravitreal triamcinolone) from the

same compounding pharmacy associated with additional patients.

Discussion

To our knowledge, this is the first systematic summary of infectious outbreaks associated with drugs compounded by pharmacies outside of the hospital setting. The reported infectious outbreaks were severe, and half involved patients in multiple states. The 2012 fungal meningitis outbreak was the largest; however, the morbidity and mortality rates were similar to those of earlier outbreaks. Patients lost their vision; required hospitalization, surgeries, or treatments; and about 7% died. Each outbreak illustrated one or more

| Contributing Factors | Scope of Product Recall |
|--|--|
| Most likely cause of outbreak was contamination during syringe preparation by the compounding pharmacy; FDA found single-use vials used for days to weeks after initial vial puncture, inadequate environmental monitoring, use of nonsterile materials, inadequate personnel training, and other deficiencies | 2 single-use vials of Avastin (bevacizumab) repackaged into 65 syringes (0.1 mL each) in 4 lots; <i>S. mitis</i> and <i>S. oralis</i> cultured from 7 unused syringes; FDA found microbial growth in 3 of 21 syringes in 2 additional lots |
| FDA found bacterial and fungal growth in International Organization for Standardization Class 5 laminar airflow hoods and ISO Class 7 cleanroom; deficiencies included inadequate personnel training, environmental monitoring, and sealing of cleanroom | 4 lots of brilliant blue-G recalled; multiple bacterial and fungal species, including <i>F. incarnatum-equiseti</i> , cultured from unused syringes. Two lots of triamcinolone acetonide 80 mg/mL recalled; 8 prescriptions in 1 lot and 5 in the other; microbial testing ongoing. Company recalled all sterile compounded products. |
| FDA inspection found multiple deficiencies, including bacteria and mold in cleanrooms used for sterile compounding, standing water near cleanroom, and airborne particulates resulting from close proximity to recycling facility; investigation is ongoing | Initial recall involved 17,676 vials from 3 lots; unopened vials in 2 lots were contaminated with <i>Exserohilum rostratum</i> . Testing of third lot is ongoing. After inspection of facility, sterility could not be ensured, so all products from NECC and sister company, Ameridose, were recalled. Three clinics in Tennessee used 1,663, 189, and 211 vials, respectively, during outbreak. In this case cluster, attack rate varied by lot involved and age of lot. |

root causes that could have been addressed with preventive policies and practices (Table 2). In particular, the literature described lapses in recommended processes for producing sterile compounded drugs and evidence that clinicians were sometimes unaware they were using compounded drugs. This lack of awareness may obfuscate links between adverse events and compounded drugs and lead to underrecognition and underreporting of problems. No single source included information about all of the outbreaks identified.

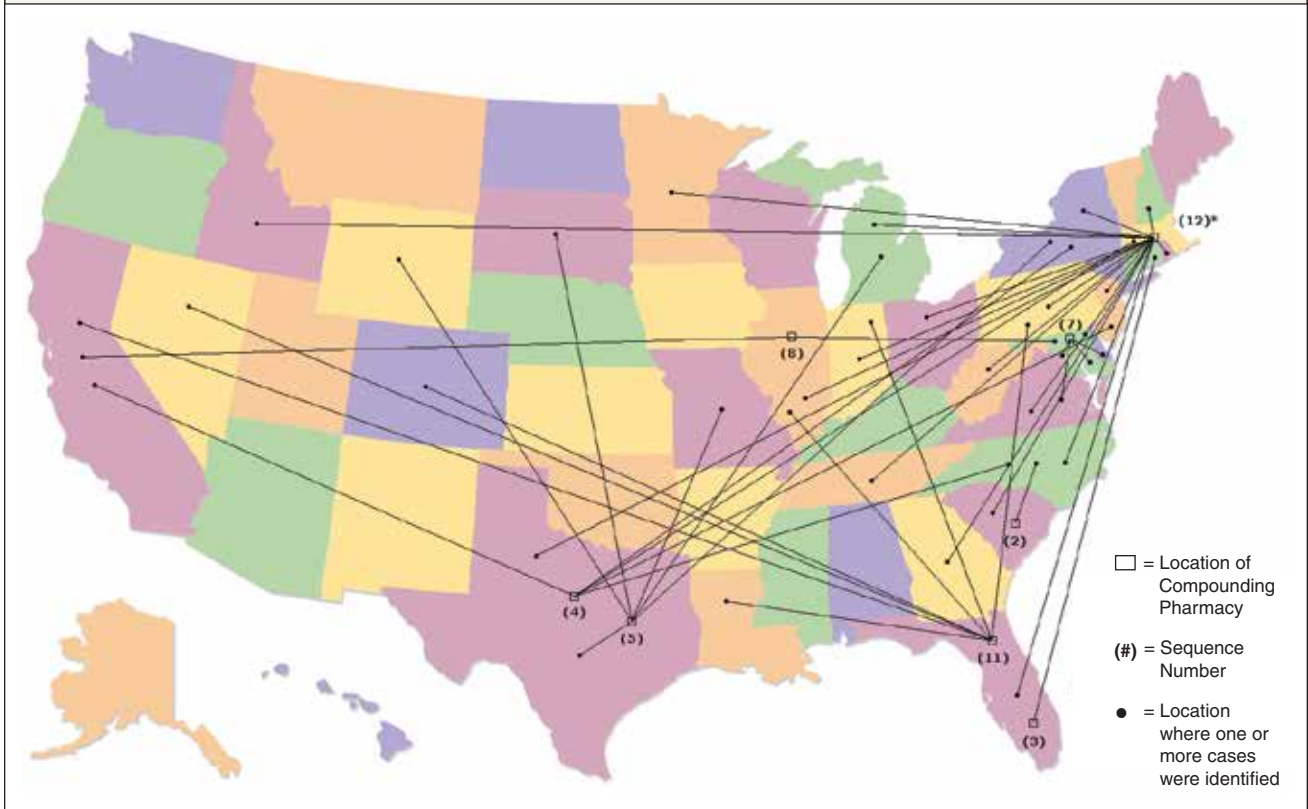
Several of the outbreaks involved suspensions or solutions that were reported to be preservative-free or were likely preservative-free, including methylprednisolone suspension (preservative status unknown; outbreak 2), preservative-free bevacizumab solution (outbreak 10), preservative-free triamcinolone (probably a suspension; outbreak 11),

and preservative-free methylprednisolone suspension (outbreak 12). Although initial publications about the 2012 fungal meningitis outbreak reported that the methylprednisolone used was a solution, congressional documents later identified it as a suspension.^{52,53} The betamethasone formulation in outbreak 1 was also likely a suspension, because it was compounded to replace an FDA-approved injectable betamethasone suspension that was not available at the time. Some compounding pharmacies market preservative-free corticosteroids for epidural injection as an alternative to FDA-approved products that contain a preservative. The rationale is that preservative-free formulations may avoid potential neurotoxicity (aseptic meningitis, arachnoiditis). Compounded drugs are also sometimes favored because of their lower costs and ready availability during shortages of com-

mercial products.^{5,30} Clinicians who use compounded preservative-free solutions and suspensions need to weigh the risks and benefits of these competing concerns.

Compounded sterile products that are preservative-free have a high risk of microbial contamination if the standards established in the *United States Pharmacopeia (USP)* for the compounding of sterile preparations (chapter 797) are not strictly followed.⁵⁸ Sterile suspensions may have a high risk of microbial contamination if inappropriate sterilization methods are used. Sterilization of suspensions by heat may not adequately remove pyrogens and fungal contaminants.⁵⁹ Likewise, sterilization by filtration may be problematic, as suspensions can clog a 0.2- μ m filter. Some experts recommend against the use of compounded injectable corticosteroid suspensions on the basis that sterilization methods avail-

Figure 1. Location of implicated compounding pharmacies and associated case patients involved in eight multistate outbreaks identified between January 2000 and November 2012.



able to compounding pharmacies are inadequate.⁵⁹

In outbreak 10, single-dose vials of preservative-free bevacizumab solution were repackaged into multiple 0.1-mL syringes for multiple patients. Some endophthalmitis outbreaks associated with compounded bevacizumab have been linked to poor aseptic technique and nonadherence to requirements for the safe repackaging of single-dose vials outlined in *USP* chapter 797.¹² CDC has taken the position that single-dose vials should only be used for one patient and advises that repackaging of unopened single-dose vials for multiple patients should only occur in times of critical need and should be performed in accordance with *USP* chapter 797.⁶⁰

The outbreaks identified in the literature were those that were inves-

tigated and reported by public health authorities after they were identified by clinicians. Investigations of reported outbreaks associated with the administration of compounded drugs were triggered when the outbreaks were associated with a cluster of unusual infections (e.g., postprocedural endophthalmitis) or when the identified organism was somehow atypical (rarely causes infection or was cultured from an unexpected site). For example, the initial report of a patient with culture-confirmed *Aspergillus fumigatus* meningitis 46 days after receiving an epidural steroid injection was sufficient to trigger active surveillance and led to the rapid recognition of additional patients with similar exposures.⁵³ This finding heralded the 2012 fungal meningitis outbreak.⁵³ Outbreaks may be more difficult to detect when

exposures and case-patients are scattered geographically or when clinical outcomes are less severe and patients have underlying conditions or treatments that could explain their outcomes. For example, even perceptive clinicians may miss compounded drugs as a source in common and expected infections, such as with central-line-associated bloodstream infections (e.g., *S. marcescens* sepsis in patients receiving total parenteral nutrition or magnesium sulfate). Lack of clinician awareness that patients even received a compounded product can be a factor that delays, or prevents, the recognition of the source of an outbreak. For example, in the *S. marcescens* bloodstream infections outbreak after cardiac surgery, neither of the hospital pharmacies was aware that the product was compounded, as “there was no

specific indication on the package labeling, and the company's website did not specify that the product was compounded.²⁸ In addition, redistribution of products from a compounding pharmacy before delivery to the final customer may limit the recognition of the potential role of compounded drugs in an infectious outbreak. For example, in the *P. fluorescens* bloodstream infection outbreak, a company employed a compounding pharmacy to make a concentrated heparin solution, which was then diluted and repackaged to make heparinized 0.9% sodium chloride injection flush syringes.³⁰ These syringes were "sold to distributors who redistributed to other medical distributors and hospitals."⁶¹ Such redistribution can blur the recognition of a common source.

To identify and link unusual infections across settings, there is a need for robust surveillance systems that support detection and reporting. Existing systems have limitations. First, communicable disease and injury reporting systems that require reporting of selected diseases and conditions to public health departments⁶² may capture events, but underreporting is common.^{63,64} In addition, the types of infections associated with contaminated compounded drugs would rely on general reporting requirements, such as "[Report] any unusual occurrence of infectious or communicable disease."⁶⁵ Even when providers recognize and consider reporting unusual events, they can be stymied by concerns about potential violations of the Health Insurance Portability and Accountability Act. Second, CDC's National Healthcare Safety Network (NHSN) includes a patient safety component, but this component would be unlikely to detect events from compounded drugs, because it focuses on the surveillance of (1) infections associated with devices or common procedures or multidrug-resistant organisms and (2) events

Table 2.

Description of Factors Identified in Infectious Outbreaks Associated With Compounded Drugs

| | |
|---|--|
| <p>Regulatory gaps</p> <ul style="list-style-type: none"> • Compliance with <i>United States Pharmacopeia</i> chapter 797 standards for compounding is voluntary. • Compounders are not required to follow good manufacturing practices established by the Food and Drug Administration. • Variation exists in state standards, enforcement, and access to enforcement reports. • Compounded drugs can be distributed across state lines. <p>Compounding processes</p> <ul style="list-style-type: none"> • Failure to maintain and monitor for a clean environment. • Personnel deviate from standard procedures or lack knowledge or skills. • Insufficient quality control (e.g., no sterility testing of final product). • Failure to act when process problems are identified. <p>Health care delivery</p> <ul style="list-style-type: none"> • Settings where exposure and follow-up occur are siloed. • Setting where exposure occurs differs from follow-up site. • Difficult to trace compounded products through health care records systems. • Compounded drugs are repackaged, relabeled, or both. | <p>Clinicians</p> <ul style="list-style-type: none"> • Unaware of regulatory gaps concerning compounded drugs • Unaware drugs being used are compounded. • Prescribe compounded agents with limited evidence for need or efficacy. • Attribute patient symptoms to other causes. <p>Patients</p> <ul style="list-style-type: none"> • Immunocompromised patients are more susceptible to infectious complications. • Drug given in high-risk site (e.g., eye, central nervous system) increases risk of complications. • Attribute adverse reactions to other sources (e.g., chemotherapy). • Unaware they are receiving a compounded product. <p>Surveillance systems</p> <ul style="list-style-type: none"> • Fail to report events not explicitly defined in reporting rules due to concerns regarding violations of the Health Insurance Portability and Accountability Act. • Focused on inpatient environment, though outpatient surveillance is increasing. • Reporting requires astute and motivated health care personnel. • Current systems focus on predefined conditions. |
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associated with dialysis and blood products.⁶⁶ NHSN is not designed to address surveillance of sporadic adverse drug events in outpatient settings and does not provide real-time reporting.

Our analysis focused on compounding pharmacies in the community rather than pharmacies that compound drugs in the hospital setting, because the former may present unique public health risks. The large scale of production and multistate distribution of products from sterile compounding pharmacies may

contribute to the size of outbreaks when they occur. In the 2012 fungal meningitis outbreak associated with NECC, approximately 17,600 doses of methylprednisolone were shipped to 76 facilities in 23 states, and an estimated 14,000 patients were exposed.⁵² As the outbreak progressed, more than 4,000 drugs made by NECC and its sister company, Ameridose, were voluntarily recalled. The volume of recalled drugs was large enough to exacerbate drug shortages.⁶⁷ The size of these companies does not appear to be an anom-

aly. Central Admixture Pharmacy Services (outbreak 7) reports making 300,000 deliveries of i.v. admixtures each year.⁶⁸ PharMEDium (outbreak 4) employs over 700 people and provides sterile compounding services to over 1,800 hospitals in 49 states.^{28,69}

This study did have limitations. In particular, the strategy used to identify outbreaks missed outbreaks not reported in the literature or investigated by FDA or CDC. For example, an EpiNotes publication by the North Carolina Department of Health commented on two patients who developed *Chryseomonas* meningitis from compounded epidural methylprednisolone in 2001, but the details are unpublished.²⁴

We recommend addressing the root causes identified in these outbreaks, including the regulatory gaps, compounding processes, awareness among clinicians, and the public health systems required to monitor compounding practices and identify and respond to outbreaks (Table 2). Compounding pharmacies should fully comply with *USP* chapter 797, the standard for sterile compounding safety in the United States.^{58,70} In 2011, state regulations had not consistently adopted *USP* chapter 797 as the standard for sterile compounding in their jurisdiction,⁷¹ and compliance among compounding pharmacies was found to be 72% among 1148 respondents from hospital settings and 82% among a limited sample of 40 respondents from community pharmacy settings.⁷² In addition, electronic health record systems should be enhanced to recognize links between compounded drugs and infections. This would require improvements in (1) real-time processing of triggers for unusual organisms, unusual organism or specimen source combinations, or rare diagnoses (e.g., endophthalmitis), (2) coding of compounded drugs in the electronic health record to identify compounded drugs, and (3) sharing of laboratory results not explicitly

defined in public health communicable disease reporting rules but indicative of unusual infections.

Conclusion

Before the nationwide 2012 fungal meningitis outbreak associated with NECC, drugs produced by compounding pharmacies were associated with 11 other outbreaks that occurred sporadically over the past 12 years. Lapses in sterile compounding procedures led to contamination of compounded drugs, exposure to patients, and a threat to public health in these outbreaks. Recognition and subsequent public health investigation were usually triggered by the occurrence of illness among multiple patients in a single health care setting.

References

1. Food and Drug Administration. Pharmacy compounding. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm (accessed 2012 Nov 2).
2. Centers for Disease Control and Prevention. Multistate fungal meningitis outbreak investigation. www.cdc.gov/hai/outbreaks/meningitis.html (accessed 2012 Nov 25).
3. Centers for Disease Control and Prevention. Multistate fungal meningitis outbreak—interim guidance for treatment. *MMWR*. 2012; 61:842.
4. Meadows M. Warnings for makers of compounded pain products. *FDA Consum*. 2007; 41(2):20-2.
5. Wilson LE, Blythe D, Sharfstein JM. Fungal meningitis from injection of contaminated steroids: a compounding problem. *JAMA*. 2012; 308:2461-2.
6. International Academy of Compounding Pharmacists responds to meningitis outbreak tied to compounding pharmacy. [www.prnewswire.com/news-releases-test/the-international-academy-of-compounding-pharmacists-responds-to-meningitis-outbreak-tied-to-compounding-pharmacy-172725431.html](http://www.prnewswire.com/news-releases/test/the-international-academy-of-compounding-pharmacists-responds-to-meningitis-outbreak-tied-to-compounding-pharmacy-172725431.html) (accessed 2013 Apr 19).
7. Romano MJ, Dinh A. A 1000-fold overdose of clonidine caused by a compounding error in a 5-year-old child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001; 108:471-2.
8. Whelan GJ, Spahn JD, Brown EE et al. Subpotency of a compounded budesonide for nebulization product in a patient with poorly controlled asthma. *J Allergy Clin Immunol*. 2006; 117(suppl):S12.
9. Burton JM, Bell CM, Walker SE et al. 4-Aminopyridine toxicity with unin-

10. Centers for Disease Control and Prevention. Deaths from intravenous colchicine resulting from a compounding pharmacy error—Oregon and Washington, 2007. *MMWR*. 2007; 56:1050-2.
11. Hundley K. Lincare pharmacy runs afoul of Missouri regulators. www.sptimes.com/2003/04/18/Business/Lincare_pharmacy_runs.shtml (accessed 2013 Apr 19).
12. Gonzalez S, Rosenfeld PJ, Stewart MW et al. Avastin doesn't blind people, people blind people. *Am J Ophthalmol*. 2012; 153:196-203.e1.
13. Chollet JL, Jozwiakowski MJ. Quality investigation of hydroxyprogesterone caproate active pharmaceutical ingredient and injection. *Drug Dev Ind Pharm*. 2012; 38:540-9.
14. Jones TF, Feler CA, Simmons BP et al. Neurologic complications including paralysis after a medication error involving implanted intrathecal catheters. *Am J Med*. 2002; 112:31-6.
15. Goldman MP. Sodium tetradecyl sulfate for sclerotherapy treatment of veins: is compounding pharmacy solution safe? *Dermatol Surg*. 2004; 30:1454-6.
16. Food and Drug Administration. Limited FDA survey of compounded drug products. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm (accessed 2012 Nov 25).
17. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: Med-South Pharmacy Inc. 28-Sep-07 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076516.htm (accessed 2012 Nov 25).
18. Sellers S, Utian WH. Pharmacy compounding primer for physicians: prescriber beware. *Drugs*. 2012; 72:2043-50.
19. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR)* homepage. www.cdc.gov/mmwr/mmwr_wk/wk_cvol.html (accessed 2012 Dec 14).
20. Centers for Disease Control and Prevention. Epidemic Intelligence Service (EIS) Conference—program archives for 2006–2012. www.cdc.gov/EIS/Conference/Archive.html (accessed 2012 Nov 10).
21. Centers for Disease Control and Prevention. Notes from the field: multi-state outbreak of postprocedural fungal endophthalmitis associated with a single compounding pharmacy—United States, March–April 2012. *MMWR*. 2012; 61:310-1.
22. Civen R, Vugia DJ, Alexander R et al. Outbreak of *Serratia marcescens* infections following injection of betamethasone compounded at a community pharmacy. *Clin Infect Dis*. 2006; 43:831-7.
23. Kastango ES. The cost of quality in pharmacy. *Int J Pharm Compd*. 2002; 6:404-7.

24. Engel J. *Exophiala* (*Wangiella*) *dermatitidis* fungal infection outbreak. <http://epi.publichealth.nc.gov/pdf/en2002-4.pdf> (accessed 2013 Apr 19).
25. Centers for Disease Control and Prevention. *Exophiala* infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July–November 2002. *MMWR*. 2002; 51:1109-12.
26. Food and Drug Administration. Injectable drugs prepared by urgent care pharmacy. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154503.htm (accessed 2012 Oct 28).
27. Held MR, Begier EM, Beardsley DS et al. Life-threatening sepsis caused by *Burkholderia cepacia* from contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. *Pediatrics*. 2006; 118:e212-5.
28. Sunenshine RH, Tan ET, Terashita DM et al. A multistate outbreak of *Serratia marcescens* bloodstream infection associated with contaminated intravenous magnesium sulfate from a compounding pharmacy. *Clin Infect Dis*. 2007; 45:527-33.
29. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: Pharmedium Services, LLC. 13-Apr-07 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076357.htm (accessed 2012 Nov 25).
30. Gershman MD, Kennedy DJ, Noble-Wang J et al. Multistate outbreak of *Pseudomonas fluorescens* bloodstream infection after exposure to contaminated heparinized saline flush prepared by a compounding pharmacy. *Clin Infect Dis*. 2008; 47:1372-9.
31. Centers for Disease Control and Prevention. *Pseudomonas* bloodstream infections associated with a heparin/saline flush—Missouri, New York, Texas, and Michigan, 2004–2005. *MMWR*. 2005; 54:269-72.
32. Centers for Disease Control and Prevention. Update: delayed onset *Pseudomonas fluorescens* bloodstream infections after exposure to contaminated heparin flush—Michigan and South Dakota, 2005–2006. *MMWR*. 2006; 55:961-3.
33. Food and Drug Administration. FDA issued nationwide alert on IV Flush brand of heparin or sodium chloride intravenous catheter flushes. www.fda.gov/downloads/ICECI/EnforcementActions/EnforcementStory/EnforcementStoryArchive/UCM091066.pdf (accessed 2012 Oct 28).
34. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: IV Flush, LLC. 04-August-05 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075511.htm (accessed 2012 Dec 16).
35. Sunenshine R, Schultz M, Lawrence MG et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. *Clin Infect Dis*. 2009; 48:1580-3.
36. Food and Drug Administration. Custom-Rx compounding pharmacy issues nationwide recall of trypan blue 0.06% ophthalmic solution. www.fda.gov/Safety/Recalls/ArchiveRecalls/2005/ucm111889.htm (accessed 2012 Nov 11).
37. Patel AS, Woolard D, McDonald LC et al. Outbreak of systemic inflammatory response syndrome linked to a compounding pharmacy—Virginia, 2005. Paper presented at the 55th Annual Epidemic Intelligence Service Conference. Atlanta, GA; 2006 Apr.
38. Food and Drug Administration. Compounded menopausal hormone therapy questions and answers. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183088.htm (accessed 2012 Nov 11).
39. Food and Drug Administration. Central Admixture Pharmacy Services, Inc.: urgent drug recall: all injectable products. www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164417.pdf (accessed 2012 Nov 11).
40. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: B. Braun Medical Inc. 15-Mar-06 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075828.htm (accessed 2012 Oct 28).
41. Maragakis LL, Chaiwarith R, Srinivasan A et al. *Sphingomonas paucimobilis* bloodstream infections associated with contaminated intravenous fentanyl. *Emerg Infect Dis*. 2009; 15:12-8.
42. Gupta N, Hocevar S, O’Cannell H et al. *Serratia marcescens* bloodstream infections in patients receiving total parenteral nutrition—Alabama, 2011. Paper presented at the 61st Annual Epidemic Intelligence Service Conference. Atlanta, GA; 2012 Apr.
43. Food and Drug Administration. CDC and ADPH investigate outbreak at Alabama hospitals; products recalled. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm249099.htm (accessed 2012 Oct 28).
44. Goldberg RA, Flynn HW Jr, Isom RF et al. An outbreak of *Streptococcus endophthalmitis* after intravitreal injection of bevacizumab. *Am J Ophthalmol*. 2012; 153:204-8.e1.
45. Matthews J, Dubovy S, Goldberg RA et al. Histopathology of streptococcal endophthalmitis following intravitreal injection of bevacizumab: a series of seven cases. Paper presented at the American Academy of Ophthalmology—Asia-Pacific Academy of Ophthalmology Annual Meeting. Chicago, IL; 2012.
46. Beau De Rochars VM, Schmitz A, Pritchard P et al. Streptococcal endophthalmitis associated with contaminated bevacizumab from a compounding pharmacy—Florida, 2011. Paper presented at the 61st Annual Epidemic Intelligence Service Conference. Atlanta, GA; 2012 Apr.
47. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: Infupharma, LLC. 7/30/12 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm317190.htm (accessed 2012 Oct 28).
48. Food and Drug Administration. FDA form 483 for Infupharma, LLC. www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM304256.pdf (accessed 2012 Dec 21).
49. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: Franck’s Lab Inc., d.b.a. Franck’s Compounding Lab. 7/9/12 (warning letter). www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm312645.htm (accessed 2012 Nov 10).
50. Food and Drug Administration. Franck’s Compounding Pharmacy sterile preparations: reports of fungal endophthalmitis, expanded recall. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm305592.htm (accessed 2012 Oct 28).
51. Centers for Disease Control and Prevention. Multistate meningitis outbreak—current case count. www.cdc.gov/hai/outbreaks/meningitis-map-large_2013-01-07.html (accessed 2013 Mar 9).
52. Committee on Energy and Commerce. Majority memorandum: hearing on “The fungal meningitis outbreak: could it have been prevented?” <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/Hearings/OI/20121114/HMTG-112-HHRG-IF02-20121114-SD001.pdf> (accessed 2012 Dec 8).
53. Centers for Disease Control and Prevention. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy—United States, 2012. *MMWR*. 2012; 61:839-42.
54. Food and Drug Administration. FDA form 483 for New England Compounding Center. www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM325980.pdf (accessed 2012 Dec 8).
55. Kainer MA, Reagan DR, Nguyen DB et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med*. 2012; 367:2194-203.
56. Centers for Disease Control and Prevention. Multistate fungal meningitis outbreak investigation: laboratory testing and results from the outbreak. www.cdc.gov/hai/outbreaks/laboratory/lab_testing_results.html (accessed 2012 Dec 16).

57. Centers for Disease Control and Prevention. Update: multistate outbreak of fungal infections among persons who received injections with contaminated medication. <http://emergency.cdc.gov/HAN/han00338.asp> (accessed 2013 Jan 21).
58. Pharmaceutical compounding: sterile preparations (general information chapter 797). In: The United States pharmacopeia, 35th rev., and The national formulary, 30th ed. Rockville, MD: United States Pharmacopeial Convention; 2012.
59. Bronstein D, Kandel S. Meningitis outbreak fallout: whom can you trust? www.painmedicineneeds.com/ViewArticle.aspx?d=Clinical+Pain+Medicine&d_id=82&i=November+2012&i_id=906&a_id=22066 (accessed 2013 Apr 19).
60. Centers for Disease Control and Prevention. Protect patients against preventable harm from improper use of single-dose/single-use vials. www.cdc.gov/injection-safety/cdcposition-singleusevial.html (accessed 2013 Jan 28).
61. Food and Drug Administration. FDA renews nationwide alert on i.v. flush brand of heparin or sodium chloride intravenous catheter flushes in light of new contamination reports. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108409.htm (accessed 2012 Nov 12).
62. Roush S, Birkhead G, Koo D et al. Mandatory reporting of diseases and conditions by health care professionals and laboratories. *JAMA*. 1999; 282:164-70.
63. Doyle TJ, Glynn MK, Groseclose SL. Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. *Am J Epidemiol*. 2002; 155:866-74.
64. Overhage JM, Grannis S, McDonald CJ. A comparison of the completeness and timeliness of automated electronic laboratory reporting and spontaneous reporting of notifiable conditions. *Am J Public Health*. 2008; 98:344-50.
65. Utah Department of Health. Disease reporting resources and information. <http://health.utah.gov/epi/report.html> (accessed 2012 Dec 15).
66. Centers for Disease Control and Prevention. Monitoring healthcare associated infections. www.cdc.gov/HAI/surveillance/index.html (accessed 2012 Nov 3).
67. Centers for Disease Control and Prevention. Voluntary recall of all Ameridose medical products. <http://emergency.cdc.gov/HAN/han00332.asp> (accessed 2012 Nov 12).
68. Central Admixture Pharmacy Services. Products and services. www.capspharmacy.com/Products.html (accessed 2012 Nov 19).
69. Harris M, Wong W. Chicago technology venture capital scorecard for 2011. http://articles.chicagotribune.com/2012-06-16/business/chi-chicago-technology-venture-capital-scorecard-for-2011-20120616_1_venture-capital-firestarter-fund-leo-capital (accessed 2013 Apr 19).
70. Kastango ES. Compounding USP <797>: inspection, regulation, and oversight of sterile compounding pharmacies. *J Parenter Enterol Nutr*. 2012; 36(suppl):38S-39S.
71. Clinical IQ. U.S. boards of pharmacy, sterile compounding laws, regulations and CE requirements map. <http://clinicaliq.com/797-state-survey> (2013 May 16).
72. Douglass K, Kastango ES, Cantor P et al. 2011 USP <797> compliance study. www.pppmag.com/article/985/ (accessed 2013 Apr 19).