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U.S. Compounding Pharmacy-related Outbreaks, 2001–2013—Public Health and Patient Safety Lessons Learned

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Abstract

Objectives—Pharmacy-compounded sterile preparations (P-CSPs) are frequently relied upon in U.S. healthcare, but are increasingly being linked to outbreaks of infections. We provide an updated overview of outbreak burden and characteristics, identify drivers of P-CSP demand, and discuss public health and patient safety lessons learned to help inform prevention.

Methods—Outbreaks of infections linked to contaminated P-CSPs that occurred between January 1, 2001 and December 31, 2013 were identified from internal Centers for Disease Control and Prevention reports, Food and Drug Administration drug safety communications, and published literature.

Results—We identified 19 outbreaks linked to P-CSPs, resulting in at least 1000 cases, including deaths. Outbreaks were reported across two-thirds of states, with almost one-half (8/19) involving cases in more than one state. Almost one-half of outbreaks were linked to injectable steroids (5/19) and intraocular bevacizumab (3/19). Non-patient-specific compounding originating from non-sterile ingredients and re-packaging of already sterile products were the most common practices associated with P-CSP contamination. Breaches in aseptic processing and deficiencies in sterilization procedures or in sterility/endotoxin testing were consistent findings. Hospital outsourcing, preference for variations of commercially available products, commercial drug shortages, and lower prices were drivers of P-CSP demand.

Conclusions—Recognized outbreaks linked to P-CSPs have been most commonly associated with non-patient-specific re-packaging and non-sterile to sterile compounding, and linked to lack of adherence to sterile compounding standards. Recently-enhanced regulatory oversight of compounding may improve adherence to such standards. Additional measures to limit and control these outbreaks include vigilance when outsourcing P-CSPs, scrutiny of drivers for P-CSP demand, and early recognition and notification of possible outbreaks.

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INTRODUCTION

The contribution of contaminated medications to serious, and at times fatal, healthcare-associated infections (HAIs) has become prominent in the United States healthcare delivery landscape. Microbial contamination of medications intended to be sterile most commonly results from infection control breaches at the point-of-care, for example when common syringes or single-use vials are shared among multiple patients. Unsafe injection practices such as these at the hospital bedside or in outpatient clinics have resulted in transmission of bacterial infections and bloodborne pathogens such as hepatitis C virus [1–3]. Upstream contamination of medications at the point-of-manufacture is rarer, but has also been reported [4,5].

Pharmacies play a crucial, intermediate role in the pathway of medications from point-of-manufacture to point-of-care, including compounding, repackaging, and labeling sterile medications, such as injectable and ophthalmic products. The Food and Drug Administration (FDA) regards compounding as the practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient [6]. Over the last two decades, pharmacies have taken on a more prominent role in compounding and re-packaging sterile products for hospitals, outpatient clinics, home health, and other healthcare settings, and sterile compounding practices have evolved to become more wide-ranging and complex [7,8]. These practices can sometimes include preparation of large quantities of sterile products in advance of prescriptions or in non-patient-specific fashion, often for distribution to multiple facilities and at times across state lines [8,9]. With this evolution in pharmacy compounding practices, new threats to patient safety have emerged.

Regulatory and professional standards for ensuring safe preparation of sterile medications have long-been established and have facilitated advancements in the quality and safety assurance of sterile compounding by pharmacies [7,8,10–12]. However, failures to adhere to these standards have been documented and these standards were not originally intended to address compounding activities at the large scale currently undertaken by some compounding pharmacies [7–9,13]. Consequently, compounding pharmacies have been increasingly identified as sources of contaminated products contributory to large and serious healthcare outbreaks [14,15]. The most prominent example of such an outbreak occurred in 2012 and involved nationwide distribution of contaminated injectable methylprednisolone acetate (MPA) [16]. This incident, one of the largest U.S. healthcare-related outbreaks on record, was characterized by nearly14,000 exposed individuals and at least 751 cases of fungal meningitis, other infections, and stroke, including at least 64 deaths across 20 states [16].

The nationwide fungal meningitis outbreak was not an isolated incident. Since 2001, the Centers for Disease Control and Prevention (CDC), along with its federal and state public health partners, have responded to and investigated numerous outbreaks of infectious illnesses linked to pharmacy-compounded sterile preparations (P-CSPs). Here, we provide an updated and expanded overview of the burden and characteristics of outbreaks linked to

P-CSPs, briefly summarize common forces driving the use of products involved in these outbreaks, and identify public health and patient safety lessons learned that could inform prevention of similar outbreaks in the future.

BURDEN OF COMPOUNDING PHARMACY-RELATED OUTBREAKS

We identified outbreaks occurring in the U.S. in which infections were linked to P-CSPs based on a search of internal data for relevant incidents reported to and investigated by CDC between January 1, 2001 and December 31, 2013. We also searched Medline, CINAHAL, and Embase databases for reports during the same time period using combinations of the terms: disease outbreaks, drug compounding, compounding pharmacy, and infectious diseases. For the purposes of this overview, sterile products that were re-packaged by compounding pharmacies (e.g., contents of an already sterile single-dose vial re-packaged into multiple syringes without undergoing any additional manipulation of the drug, such as sterilization, at the pharmacy) were also considered P-CSPs. Food and Drug Administration notices of compounding pharmacy regulatory actions and publicly-available pharmacy inspection reports were also reviewed and used to obtain details regarding lapses in sterile compounding procedures that may have contributed to P-CSP contamination [17]. Information about clinical drivers for P-CSP demand was based on descriptions of indications for which compounded products were being used as provided in outbreak and related reports, as well as published literature.

We excluded outbreaks linked to products prepared in hospital pharmacies that were not identified as institutional compounding pharmacies [18,19] and products prepared in specialty (e.g., nuclear) pharmacies [20], outbreaks where the source of contamination was extrinsic (e.g., product contamination due to mishandling at the bedside) [1]. Also excluded were CSP contamination incidents that did not result in infectious illnesses (e.g., those that led solely to pharmacy inspections, warning letters, or product recalls, but no reported infections) and incidents related to compounding pharmacy dispensing errors (e.g., errors in dosage calculation or mistaken active ingredients) [21–23], intentional adulteration [24], or veterinary medicines [25].

We identified 19 U.S. outbreaks since 2001 that were linked to contaminated medications prepared by compounding pharmacies [16,26–50]. These incidents were associated with a range of 2 to 751 cases (Table 1); almost one-half (8/19) of these incidents involved deaths possibly related to exposure to contaminated P-CSPs [16,26,28,32,36,41,45,50]. The exact numbers of CSPs dispensed or distributed each year by compounding pharmacies is not known, but the current figure is likely in the tens of millions [51], with at least two-thirds of U.S. hospitals reporting reliance on outside pharmacies for CSPs [52,53]. Although the number of recognized outbreaks linked to contaminated P-CSPs can be considered relatively small given these figures, these incidents are being reported with an increased frequency [14,15]. Additionally, these outbreaks have often resulted in devastating consequences to patients, including serious adverse events such as blindness and life-threatening sepsis, a need to institute additional medical and procedural interventions, and fatalities [16,26,28–32,36,39,41–43,45,50].

The number of recognized outbreaks linked to contaminated P-CSPs should also be viewed as an underestimate for a number of reasons (Table 2). First, identification of healthcare outbreaks linked to contaminated medications, including P-CSPs, is challenging as identification relies on clinician recognition of a possible link between clusters of infections and a potentially contaminated product, followed by prompt reporting to public health authorities [4,54]. Outbreaks linked to P-CSPs, especially, present numerous challenges, as they have often involved products that are ubiquitous in healthcare settings (e.g., electrolyte solutions) (Table 1), thus clinicians may not readily recognize the medication as a potential source of infections. Further challenging clinician recognition of a link between a contaminated compounded product and an infection is the fact the most pathogens that have contributed to P-CSP contamination incidents to date, such as *Pseudomonas spp.* and *Serratia spp.*, are common causes of infections that patients acquire during exposure to healthcare for a multitude of reasons other than exposure to contaminated medications [55]. Delayed presentation of infectious symptoms after exposure to contaminated P-CSPs has also been reported with certain types of contaminants (e.g., fungal pathogens) [43,56] and routes of administration (e.g., via indwelling catheter) [33], which can also potentially delay identification of an outbreak.

Second, compounding pharmacies have been increasingly engaging in multi-facility and multi-state distribution of large quantities of sterile products [8,9], such that patients exposed to contaminated P-CSPs could present in widespread and disparate fashion. This poses additional challenges in finding a common link if there are only small clusters of infections across a number of healthcare settings [16,43]. For example, in one recent investigation of endophthalmitis infections linked to compounded Brilliant Blue Green intraocular dye, a cluster of infections reported from one facility prompted enhanced nationwide case finding that identified a second, previously unrecognized outbreak of endophthalmitis linked to compounded ophthalmic triamcinolone prepared by the same pharmacy [43].

Third, except for facilities that voluntarily register with FDA as outsourcing facilities, a new category of compounders created by the Compounding Quality Act enacted in November 2013 [57], compounding pharmacies generally do not report adverse events from CSPs to the FDA. Since the onset of the 2012 fungal meningitis outbreak associated with contaminated MPA [16,44], numerous compounding pharmacies have voluntarily conducted nationwide recalls of other CSPs [17]. Although some of these recalls involve P-CSPs linked to already recognized outbreaks, the possibility that other contaminated P-CSPs have contributed to infections that have gone undetected cannot be excluded. For these reasons, the true burden of HAIs from contaminated P-CSPs is likely higher than is suggested by the numbers of outbreak cases or fatalities identified to date.

CHARACTERISTICS OF COMPOUNDING PHARMACY-RELATED OUTBREAKS

Contaminated P-CSPs have originated from 13 states, with 31 states and D.C. reporting outbreak cases [16,26–50]. Patients receiving healthcare in various settings, including hospitals, outpatient clinics, ambulatory surgery centers, and home healthcare have been impacted (Table 1). Almost one-half of recognized outbreaks followed spinal/paraspinal (e.g., epidural), peripheral joint, or intramuscular administration of the steroids

betamethasone or methylprednisolone (5/19) [16,26–29,44,46], or intraocular administration of the monoclonal antibody bevacizumab (3/19) [39,42,44,48]. The large contribution of steroids to compounding pharmacy-related outbreaks is likely a reflection of several factors. These include the widespread use of preservative-free steroid compounding to meet increased demand for epidural injections [58] and elevated risk of infection among recipients of epidural steroid injections imparted by immunosuppressive properties of steroid medications, route of drug administration, and underlying clinical characteristics of the patients receiving them (e.g., older age) [44,56]. The complexity associated with compounding steroid solutions, which frequently requires sterilization of non-sterile bulk active ingredients to produce a final sterile solution, also likely contributes to increased potential for contamination of this product [59].

The most commonly identified pathogens in infections linked to contaminated P-CSPs have been gram-negative bacteria (e.g., *Pseudomonas spp.* and *Serratia spp.*) (10/19) [26,27,30,33–36,41,45,46]. Infections associated with contaminated P-CSPs most commonly manifested as bacteremia (7/19) [30,33,34,36,41,45,50], endophthalmitis (5/19) [35,39,42,43,48], and meningitis (4/19) [16,26–29]. Other reported infections included: other spinal/paraspinal infections (e.g., epidural abscesses), joint infections, sepsis/systemic inflammatory response syndrome, skin and soft tissue infections, and flu-like symptoms (Table 1).

Contamination of P-CSPs leading to recognized outbreaks has been linked to deviations from established sterile compounding standards [16,26–29,31,34,39,41,42–50,59–67]. The United States Pharmacopeial Convention (USP) National Formulary Chapter <797> is a compendium of standards that describes practices intended to minimize the potential for microbial, chemical, and physical contamination during sterile pharmaceutical compounding across the domains of personnel competency, environmental quality and control, and quality assurance practices [10]. In outbreaks linked to P-CSPs to date, breaches in practices across all these domains have been identified (Table 3). Practices that involve manipulations of previously sterile (usually commercially manufactured) products, such as combining the contents of two commercially manufactured vials into a single syringe, are typically referred to as sterile to sterile compounding [10]. Non-sterile to sterile compounding typically comprises such practices as preparation of a final sterile product from non-sterile ingredients [10]. Breaches have been identified with both “sterile to sterile” and “non-sterile to sterile” compounding practices (Table 1).

Although all types of sterile compounding practices inherently possess the potential for contamination, approximately two-thirds (11/16) of the recognized outbreaks linked to P-CSPs (for which information about compounding procedures was available) have been associated with non-sterile to sterile compounding [16,26,28,33,35,41,43,45,46,49,50,59,63,64,66,67]. In this type of compounding practice, properly conducted and validated sterilization processes are critical for ensuring the sterility and integrity of the final product. Sterilization of CSPs that originate from non-sterile ingredients can be achieved by filtration or autoclaving (sterilization by way of pressurized steam) [10]. Outbreaks associated with non-sterile to sterile compounding have in common deviations in these sterilization procedures [16,26,28,41,46,49,50,59,64,66,67]. Examples of

such deviations have included failing to verify the integrity of the sterilization filter, to test autoclave effectiveness, to autoclave CSPs for appropriate periods of time, and to appropriately validate the sterilization processes [26,28,41,59,66,67]. Deficiencies in aseptic practices occurring prior to or after the sterilization process have also been documented in outbreaks linked to contaminated P-CSPs compounded from non-sterile ingredients [43,45,50,59,64,66,67].

Outbreaks involving non-sterile to sterile compounding have also been linked to failing to perform adequate sterility and endotoxin testing of the final product [28,33,35,41,45,59,66,67]. Compounding pharmacies can outsource CSP sterility testing to independent laboratories; in at least one outbreak to date [16,59], quality control procedures at such a laboratory were found to be not in accordance with accepted standards [68]. Additionally, in 2013, the FDA issued warnings about the adequacy of CSP quality and sterility testing at another laboratory utilized by over 100 compounding pharmacies across 32 states [69].

DRIVERS OF STERILE COMPOUNDING IN THE CONTEXT OF OUTBREAKS

Underlying the recognized outbreaks linked to P-CSPs are common driving forces for sterile pharmaceutical compounding that have served to catalyze and potentiate the impact of these incidents. Broadly, these drivers can be categorized as operational, clinical, and economic.

Operational Drivers

Since 2001, recognized outbreaks linked to P-CSPs have impacted patients in both inpatient and outpatient settings (Table 1). In inpatient settings, during the past two decades, operational driving forces have stimulated an increased reliance by U.S. hospitals on sterile medication preparation by outside pharmacies [7,8,52,53]. The shift to outsourced sterile medications on the part of hospitals was partially driven by a need to adopt more rigorous, complex, and standardized methods of preparing sterile medications, especially those used in high volumes and in customized dosage forms (e.g., electrolytes, anesthesia, parenteral nutrition, catheter flush solutions) [7,8,70,71]. In outpatient settings, the growth of independent ambulatory care specialty practices (e.g., ambulatory surgery centers and pain clinics) that frequently use sterile medications in high-risk procedures (e.g., epidural injections) has also stimulated an increased reliance on compounded sterile preparations [58,72,73]. Most of these types of outpatient settings are not equipped with the facilities or personnel required for safely preparing sterile medications and thus rely on compounding pharmacies to meet the demand for sterile products.

Clinical Drivers

Clinical demand for medications that have not been readily available through commercial channels is among the most important drivers for CSPs involved in compounding pharmacy-related outbreaks. To date, almost one-half (9/19) of outbreaks linked to P-CSPs have involved sterile products that compounding pharmacies were supplying in response to lack of availability of a commercially manufactured product [16,26–28,41,43,44,46,49,50,74–76], owing to either a commercial drug shortage (e.g., calcium gluconate) or demand for a

formulation of a product slightly different than what is available from conventional manufacturers (e.g., preservative-free steroids).

Clinical Drivers – Drug Shortages

Over the past few years, the U.S. has been facing unprecedented numbers of medication shortages, with the number of shortages tripling between 2007 and 2012 [77]. A recent government report estimated that from June 2011 to June 2013, generic sterile injectable medications, including those critical for day-to-day care of acutely ill or hospitalized patients (e.g., antibiotics, electrolytes, antineoplastics), accounted for almost one-half of shortages where alternative medicines were not available or the shortages affected multiple manufacturers and institutions [77]. Compounding pharmacies have responded to these shortages by preparing sterile injectable products from raw active ingredients. In a survey of a nationally-representative sample of acute care hospitals that participated in Medicare in 2012, approximately two-thirds of respondents cited commercial drug shortages as an important factor when deciding to outsource CSPs [53]. Of notable concern, one recent FDA report found that, among manufacturers of veterinary medicines (for which shortages are also a concern), a return to production has been made less likely owing to manufacturers being concerned that the market share for their products has already been met by compounding pharmacies [78].

Clinical Drivers – Provider Demand

In contrast to drug shortages, other compounding pharmacy-related outbreaks have involved medications for which commercially available products are available, but do not quite meet providers' clinical preferences. This is best illustrated by the outbreaks related to injectable steroids [16,26–28,44,46], the products that have most commonly associated with compounding pharmacy-related outbreaks to date. In most incidents, clinicians were seeking steroids without preservatives typically found in FDA-approved, manufactured equivalents, most commonly for off-label use in epidural injections [16,26,27–29,44]. Use of preservative-free steroids is preferred owing to long-held concerns regarding potential harms associated with preservatives administrated into central nervous system spaces [79]. Pharmacy-compounded injectable steroids for epidural injections can also meet clinicians' preferences for these products in concentrations and volumes preferred for epidural injection, which can vary widely across practices and clinicians [80].

Economic Drivers

One important, but poorly-explored, driver of providers seeking CSPs in lieu of manufactured equivalents is the differential pricing between CSPs and commercial products [81–83], illustrated by the outbreaks linked to repackaging of bevacizumab [39,42,48]. Bevacizumab (Avastin®, Genentech/Roche) is a recombinant monoclonal antibody that is FDA-approved as a chemotherapeutic agent and is packaged in a single-use preservative free vial. Repackaged bevacizumab has been widely adopted among ophthalmology providers for off-label, intraocular treatment of wet age-related macular degeneration (AMD), the leading contributor to vision loss among older Americans [83]. A manufactured alternative to bevacizumab that is FDA-approved for the treatment of AMD (ranibizumab, Lucentis®) is available in sizes suitable for intraocular administration; however, re-packaged bevacizumab

has study-confirmed similarities to ranibizumab [84] and an approximately 40-fold cost difference exists between the two agents—$2,023 per dose for ranibizumab compared to $55 per dose for bevacizumab [83,85].

Off-label use of bevacizumab for intraocular administration typically involves splitting a single bevacizumab vial into smaller doses suitable for intraocular administration in a single eye [86]. Because bevacizumab is supplied by the manufacturer in preservative-free formulation intended for single-use only, as with all sterile medications, repackaging requires extreme care to avoid contamination of the original vial and the syringes into which the medication is partitioned [86]. Re-packaging of bevacizumab under inadequate conditions to ensure sterility may pose a risk to a very high number of patients because compounding pharmacies are sometimes preparing tens to hundreds of thousands of bevacizumab syringes annually. Across all bevacizumab-related outbreaks to date, deviations from the processes critical for ensuring safe re-packaging of bevacizumab have been documented [38,39,42,47,48,62,65].

PUBLIC HEALTH AND PATIENT SAFETY LESSONS LEARNED

This overview of recognized compounding pharmacy-related outbreaks points to salient targets that can be addressed by public health authorities, regulators, compounders, and clinicians in efforts to prevent similar outbreaks from occurring in the future. First, almost all outbreaks linked to contaminated P-CSPs have been associated with non-patient-specific production practices that have gone beyond the original intent of pharmacy compounding—compounding by a pharmacist, in response to a prescription, for an individual patient [6]. The recent passage of the Compounding Quality Act after the 2012 nationwide meningitis outbreak is expected to facilitate more rigorous federal oversight of facilities engaged in this type of compounding [57]. Compounding facilities that voluntarily elect to register as “outsourcing facilities” will be subject to requirements and oversight more closely resembling those applicable to drug manufacturers, such as compliance with standards more aligned with those for pharmaceutical manufacturing [87], mandatory reporting of adverse drugs events to the FDA, and inspections of their facilities by the FDA according to a risk-based schedule [57]. The FDA has recently recommended that healthcare facilities that outsource preparation of sterile products obtain CSPs only from registered outsourcing facilities [88].

Second, with the passage of the Compounding Quality Act, there will remain a category of pharmacies engaged in more traditional compounding practices that are not subject to the same standards as those for outsourcing facilities. For these pharmacies, there remains the need to address poor adherence to sterile compounding standards that have been consistently identified across recognized outbreaks linked to P-CSPs. Compliance with sterile compounding standards, including those of USP Chapter <797>, is known to be highly variable [13,89]. Currently, not all state public health departments or boards of pharmacy uniformly incorporate USP Chapter <797> guidelines into state laws that govern pharmacy practice [90]. State public health departments and boards of pharmacy can play a critical role in facilitating more uniform application of and adherence to professional and regulatory compounding standards. Clarifying federal versus state oversight roles, improving state

resources and staffing to allow for adequate oversight, and enhancing communication between state and federal oversight bodies have been identified as important opportunities to strengthen public health protection from contaminated P-CSPs at the state level [91]. Improving professional and technical competencies of pharmacists and other providers in sterile compounding practices within didactic curriculums and experiential settings has also been recommended to help enhance knowledge of and adherence to sterile compounding standards [92,93].

Third, only a few commonly used sterile injectable products (preservative-free steroids and bevacizumab) formulated or re-packaged for off-label uses were responsible for the overwhelming majority of compounding pharmacy-related outbreaks, suggesting that better scrutiny of the drivers for demand of these products is warranted. For example, the use of epidural steroid injections for the treatment of chronic back pain is considered to be highly controversial owing to a paucity of evidence to support long-term benefits and recognized risks associated with administration of steroids by the epidural route [79,94–97]. Nevertheless, epidural steroid administration remains one of the most commonly utilized approaches to chronic low back pain treatment and the most commonly performed interventional pain procedure in the U.S., with millions of these procedures performed each year [58,96,98].

Likewise, the off-label use of bevacizumab for the treatment of wet AMD in lieu of its commercially manufactured counterpart has been increasingly explored as a means of achieving savings for Medicare and patients in the billions of dollars [83,85]. However, the safeguards necessary to ensure that bevacizumab is re-packaged safely for the purposes of intraocular administration have not been uniformly applied by compounding pharmacies [38,39,42,47,48,62,65]. National shortages of commercially manufactured products were an additional driver underlying the demand for P-CSPs in recognized outbreaks [26–28,41,50]. Manufacturer shortages of sterile medications that are critically relied upon across healthcare settings is currently receiving national attention from regulators and healthcare policy-makers, and attempts at mitigating the negative impact of these shortages on patient care are actively being explored [77,78].

CONCLUSIONS

As compounding pharmacies continue to play a prominent role in preparation and distribution of sterile pharmaceuticals across U.S. healthcare settings, the number, impact, and severity of infectious risks and outbreaks secondary to potentially contaminated CSPs may increase. Recognized outbreaks linked to compounding pharmacies have been most commonly associated with non-patient-specific re-packaging of sterile products and non-sterile to sterile compounding. These practices were consistently characterized by lack of adherence to regulatory and professional standards for sterile compounding, suggesting that outbreak incidents are likely highly preventable with improved oversight of and adherence to such standards. Given the recent passage and ongoing implementation of the Compounding Quality Act, it is unclear what impact the new regulatory oversight framework will have in preventing these outbreaks. Regardless, improving compounding personnel competency, strengthening environmental quality controls, and implementing rigorous quality assurance

processes, especially during non-patient-specific compounding, will be critical for ensuring the safety of patients receiving compounded sterile medications. Drivers for P-CSP demand, such as off-label uses and lower costs, warrant closer scrutiny. Strong federal and state public health partnerships, as well as early recognition and notification of possible outbreaks on the part of clinicians, will continue to be critical in facilitating rapid identification and control of these types of outbreaks.

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Table 1

Recognized Outbreaks of Infections Illnesses Linked to Products Prepared by Compounding Pharmacies, United States, 2001–2013[*]

Date of Outbreak (Year)	Location of Pharmacy (State)	Location(s) of Outbreak Cases (State)	Healthcare Setting(s) Where Product(s) Received	Contaminated Product(s)	Route(s) of Product Administration	Reason for Compounding/Use	Type of Compounding	Infection Type (No. of Outbreak Cases)	Organism(s)
2001 [26]	CA	CA	Ambulatory surgery center	Betamethasone	Epidural, peripheral joint injection	Commercially unavailable (drug shortage), off-label use	Non-sterile to sterile	Meningitis (5), epidural abscess (5), hip septic arthritis (1)	*Serratia marcescens*
2002 [27]	MI	MI	Unknown	Methylprednisolone	Epidural injection	Commercially unavailable (drug shortage), off-label use	Unknown[†]	Meningitis (2)	*Chryseomonas (Pseudomonas) luteola*
2002 [28,29]	SC	NC	Pain clinic	Methylprednisolone	Epidural, sacroiliac injection	Commercially unavailable (drug shortage), off-label use	Non-sterile to sterile	Meningitis (4), sacroiliitis (1), lumbar discitis (1)	*Exophiala dermatitidis*
2004 [30]	FL	CT	Home health	Heparin-vancomycin	Catheter flush	High-volume acute care product	Unknown	Bacteremia/ sepsis (2)	*Burkholderia cepacia*
2004–2005 [31,32,60]	MD	VA	Hospital (inpatient)	Cardioplegia	Coronary infusion	High-volume acute care product	Sterile to Sterile	Systemic inflammatory response syndrome (11)	Unknown[‡]
2004–2006[§] [33]	TX	MI, MO, NY, SD, TX, WY	Inpatient, Outpatient, Home health	Heparin-sodium chloride	Catheter flush	High-volume acute care product	Non-sterile to sterile	Bacteremia (80)	*Pseudomonas spp.*
2005 [34,61]	TX	CA, MA, NC, NJ, NY, SD	Hospital (inpatient)	Magnesium sulfate	Intravenous injection	High-volume acute care product	Sterile to Sterile (Re-packaging)	Bacteremia (18), sepsis (1)[//]	*Serratia marcescens*
2005 [35]	MN	D.C., MN	Ophthalmology surgery	Trypan blue	Intraocular injection	High-volume surgery product	Non-sterile to sterile	Endophthalmitis (6)	*Pseudomonas aeruginosa*, *Burkholderia cepacia*
2007 [36,37]	MS (suspected)	CA, MD	Hospital (inpatient)	Fentanyl	Intravenous injection	High-volume acute care product (custom concentration)	Unknown	Bacteremia (8)	*Sphingomonas paucimobilis*
2009–2010 [38–40]	TN	TN	Ophthalmology clinic	Bevacizumab	Intraocular injection	High-volume surgery product, re-packaging, off-label use	Sterile to Sterile (Re-packaging)	Endophthalmitis (5)[¶]	Alpha-hemolytic *Streptococcus*
2011 [41]	AL	AL	Hospital (inpatient)	Total parenteral nutrition	Intravenous injection	High-volume acute care product (drug shortage of amino acids component)	Non-sterile to sterile	Bacteremia (19)	*Serratia marcescens*
2011 [42,62]	FL	FL	Ophthalmology clinic	Bevacizumab	Intraocular injection	High-volume surgery product, re-packaging, off-label use	Sterile to Sterile (Re-packaging)	Endophthalmitis (12)	*Streptococcus mitis/oralis*
2011–2012 [43,63]	FL	CA, CO, IL, IN, LA, NC, NV, NY, TX	Ambulatory surgery center	Brilliant Blue Green (BBG), Triamcinolone	Intraocular injection	Commercially unavailable, off-label use (BBG)	Non-sterile to sterile	Endophthalmitis (47 total; BBG: 21; Triamcinolone: 26)	*Fusarium incarnatum-equiseti*, *Bipolaris hawaiiensis*

Date of Outbreak (Year)	Location of Pharmacy (State)	Location(s) of Outbreak Cases (State)	Healthcare Setting(s) Where Product(s) Received	Contaminated Product(s)	Route(s) of Product Administration	Reason for Compounding/Use	Type of Compounding	Infection Type (No. of Outbreak Cases)	Organism(s)
2012 [16,44,59,74]	MA	FL, GA, ID, IL, IN, MD, MI, MN, NC, NH, NJ, NY, OH, PA, RI, SC, TN, TX, VA, WV	Various	Methylprednisolone	Spinal (e.g., epidural, nerve root block), paraspinal (e.g., sacroiliac), peripheral joint injection	Commercially unavailable in desired form (i.e. preservative-free), off-label use	Non-sterile to sterile	Meningitis, other spinal/paraspinal infection (e.g., epidural abscess), peripheral joint infection (751) **	*Exserohilum rostratum, Aspergillus fumigatus, other fungi*
2012# [45]	NC	NC	Hospital (inpatient)	Fentanyl	Intravenous injection	High-volume acute care product	Non-sterile to sterile	Bacteremia (7)	*Burkholderia cepacia*
2012–2013 [46,64]	TN	AR, FL, IL, NC	Various	Methylprednisolone	Intramuscular injection	Commercially unavailable in desired form (i.e. preservative-free), off-label use	Non-sterile to sterile	Skin and soft tissue infection (26)	*Enterobacter cloacae, Klebseilla pneumoniae, Aspergillus spp.*
2013 [47,48,65]	GA	GA, IN	Ophthalmology clinic	Bevacizumab	Intraocular injection	High-volume surgery product, re-packaging, off-label use	Sterile to Sterile (Re-packaging)	Endophthalmitis (5)	*Granulicatella adiacens, Abiotrophia spp.*
2013 [49,66,75]	TX	TX	Unknown	Methylcobalamin	Intravenous injection	Commercially unavailable, off-label use	Non-sterile to sterile	Fever, flu-like symptoms, chills (6)	Unknown
2013 [50,67,76]	TX	TX	Hospital (inpatient)	Calcium gluconate	Intravenous injection	Commercially unavailable (drug shortage)	Non-sterile to sterile	Bacteremia (15)	*Rhodococcus equi*

* Excludes outbreaks linked to products prepared in hospital-based pharmacies not identified as institutional compounding pharmacies or in specialty (e.g., nuclear) pharmacies and outbreaks where the source of contamination was extrinsic (e.g., product contamination due to mishandling at the bedside). Also excluded are contamination incidents that did not result in infectious illnesses and incidents related to compounding pharmacy dispensing errors (e.g., errors in dosage calculation or mistaken active ingredients), intentional adulteration, or veterinary medicines. Date of outbreak refers to the year(s) in which outbreak cases were defined in that report. Route of product administration refers to route of exposure among outbreak cases (product may have been used in other ways in non-outbreak cases). Organism(s) refers to the pathogens identified among some or all outbreak cases, not necessarily the pathogens identified in the compounded product.

† Centers for Disease Control and Prevention, unpublished data. “Re-sterilization” of product reported to have been carried out by the compounding pharmacy [27].

‡ *Enterobacter spp., Pseudomonas spp.,* and *Serratia spp.* and other gram negative bacteria identified in unopened bags of cardioplegia solution [32].

§ Compounding carried out by a compounding pharmacy in conjunction with a manufacturer. Sterilization of non-sterile ingredients carried out by the compounding pharmacy [33].

‖ One additional case in South Dakota identified from Food and Drug Administration Warning Letter [61].

¶ Only five of the nine cases described in this report are shown here as four cases were later linked to a hospital pharmacy, not a compounding pharmacy [40].

** Includes seven cases of stroke without lumbar puncture to confirm infection [16].

Institutional compounding pharmacy [45].

Table 2

Challenges in Detection of Outbreaks of Infectious Illnesses Linked to Products Prepared by Compounding Pharmacies

- Compounded sterile preparations not readily recognized as potential sources of contamination
  - Medications involved may be commonly utilized in healthcare settings
  - Pathogens involved may be common causes of HAIs
- Presentation of infectious illness can be delayed depending on the pathogen (e.g., fungal pathogen with long incubation period) or site of exposure/infection (e.g., indwelling catheter)
- Cases present to multiple facilities and providers owing to multi-facility and/or multi-state distribution of compounded sterile preparations
- Mandatory reporting of adverse drug events from compounded sterile preparations to FDA by compounding pharmacies historically has not been required *

* The passage of the Compounding Quality Act on November 27, 2013 created a new category of FDA-registered outsourcing facilities; these facilities will be subject to certain FDA reporting requirements, including reporting of adverse events from compounded products to the FDA.

Abbreviations: FDA = Food and Drug Administration; HAI = Healthcare-associated infection.

Table 3

Examples of Common Deviations from Sterile Compounding Standards in Recognized Outbreaks of Infectious Illnesses Linked to Products Prepared by Compounding Pharmacies, United States, 2001–2013

Compounding Practice Domain	Example Deviations in Standard Practices
Personnel Competency	• Lack in qualifications or training of compounding personnel • Poor PPE practices (e.g., gowning, gloving, masking) • Poor aseptic practices (e.g., contamination of syringes, needles, and clean space; use of single-use vials as multi-use vials) • Lack of personnel follow-up, corrective actions • Lack of documentation of personnel competency
Environmental Quality and Control	• Lack of adherence to USP Chapter <797> clean room specifications • Introduction of materials from uncontrolled environments into clean work spaces • Lack of adequate environmental monitoring (air, surface, personnel) • Lack of real-time temperature monitoring • Lack of documentation of maintenance and cleaning logs of major equipment • Reliance on sub-standard base ingredients • Lack of visible instructions for equipment use and troubleshooting • Conflicting labeling/documentation of sterile vs. non-sterile raw materials
Quality Assurance	• Inadequate sterilization (e.g., filtration, autoclaving) procedures • Inadequate or no sterility, endotoxin testing • Limited to no follow-up on sterility or endotoxin testing • Release of product prior to sterility or potency assurance • Storage practices unsupported by safety or efficacy data • Beyond use dating unsupported by stability or sterility data

Abbreviations: PPE = Personal Protective Equipment; USP = United States Pharmacopeial Convention.