Sterile Compounding: Clinical, Legal, and Regulatory Implications for Patient Safety

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ABSTRACT

BACKGROUND: Poor compounding practices by the New England Compounding Center resulted in the 2012-2013 fungal infections outbreak. Contaminated injectable methylprednisolone led to the diagnosis of fungal infections in 751 patients and 64 deaths. In the United States, pharmacy compounding has traditionally been regulated by state boards of pharmacy rather than the FDA. To minimize safety risks related to pharmacy compounding, the Drug Quality and Security Act (DQSA) was signed into law November 27, 2013, to improve regulation of compounding pharmacies.

OBJECTIVES: To (a) review the literature regarding clinical, legal, and regulatory implications of pharmacy compounding for patient safety during the 2012-2013 fungal infections outbreak and (b) discuss strategies that managed care organizations (MCOs) can use to promote safe compounding practices.

METHODS: A literature search was conducted via PubMed for original articles on fungal infections related to drug compounding published October 2012 to March 2014. Specific search terms included "drug compounding and fungal infection" and "fungal meningitis outbreak." The FDA website was also utilized for material related to the Food, Drug, and Cosmetic Act and the DQSA.

RESULTS: Four articles met inclusion criteria. The 2012-2013 fungal infections outbreak was attributed to 3 lots of preservative-free methylprednisolone acetate, which comprised 17,675 vials distributed to 76 facilities across 23 states. Median incubation period (from time of last injection to initial diagnosis) was 47 days, ranging from 0 to 249 days. According to the FDA, a total of 30 recalls regarding compounded products were issued by pharmacies during March through December 2013.

CONCLUSIONS: Pharmacy compounding has the potential for significant safety risks. The purpose of the DQSA is to improve regulation of compounding pharmacies. Since registration as an outsourcing facility is voluntary, uncertainty still remains regarding advancement in safe compounding practices. MCOs can employ multiple strategies to ensure patient safety and promote appropriate drug therapy.

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What is already known about this subject

- The 2012-2013 fungal infections outbreak is the largest outbreak of health-care associated infections in the United States and was attributed to injectable methylprednisolone, compounded by the New England Compounding Center in Massachusetts.
- In the United States, pharmacy compounding has traditionally been regulated by state boards of pharmacy rather than the FDA.
- The Drug Quality and Security Act (DQSA) created a new class of manufacturers known as "outsourcing facilities," for compounders that voluntarily register with the FDA under section 503B of the Food, Drug, and Cosmetic (FD&C) Act.

What this study adds

- A comprehensive summary of the clinical, legal, and regulatory implications of drug compounding for patient safety is provided, addressing the DQSA, sections 503A and 503B of the FD&C Act, the FDA website, and the primary literature.
- Traditional compounding and sterile compounding are regulated by the FD&C Act under sections 503A and 503B, respectively, and thus are subject to different exemptions, regulatory oversight, and facility and prescription requirements.
- Managed care organizations have many factors to consider regarding management of compounded drug products, such as safety and efficacy supporting use for a specific indication, quality assurance, qualifications of the pharmacy such as registration with the FDA, and cost of bulk ingredients.

The 2012-2013 outbreak of fungal infections across the United States reinforced existing concerns related to pharmacy compounding practices. The origin of the infections was traced back to injectable methylprednisolone, compounded by the New England Compounding Center (NECC) in Massachusetts.[1] The NECC's poor quality control resulted in the diagnosis of fungal infections in 751 people and resulted in 64 deaths, with Michigan reporting the greatest number of confirmed cases, followed by Tennessee.[2]

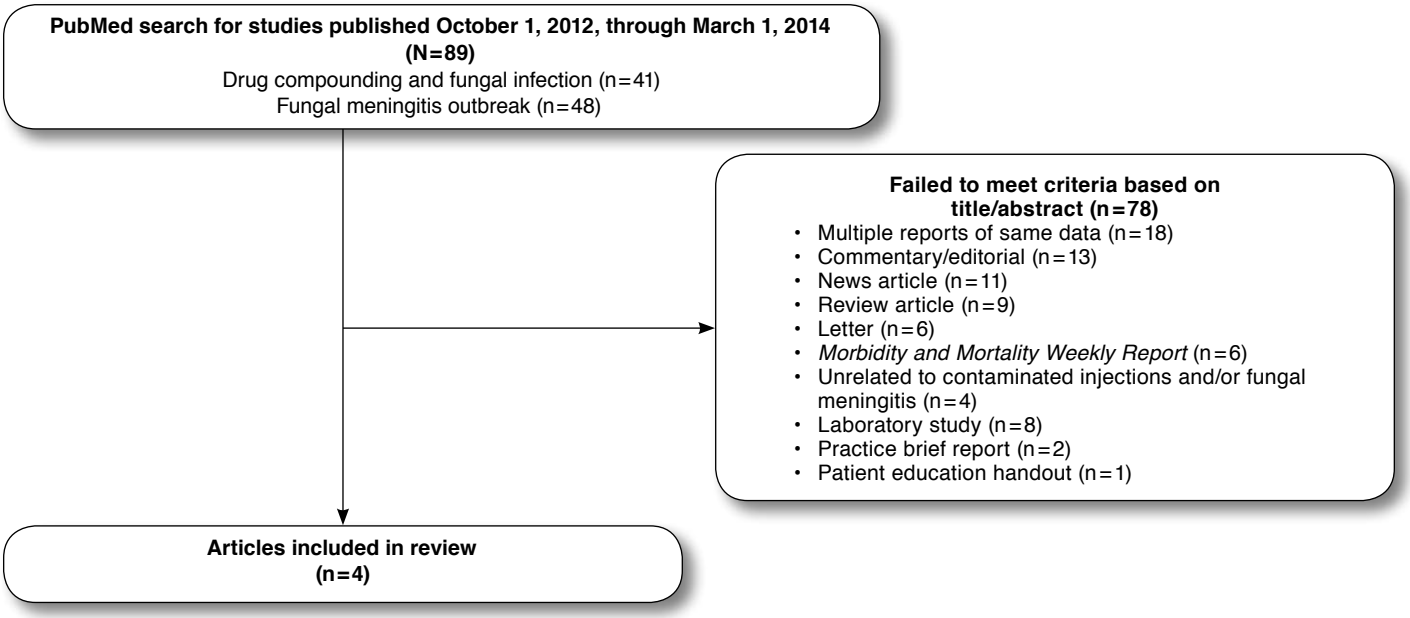
Compounding is defined differently by the U.S. Food and Drug Administration (FDA) and the United States Pharmacopeial (USP) Convention (Table 1). Under the Food, Drug, and Cosmetic (FD&C) Act, the FDA defines compounding in sections 503A (pharmacy compounding) and 503B (outsourcing facilities). Section 503A lacks a clear definition of compounding, whereas section 503B is more specific by explicitly stating that "the term 'compounding' includes the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug."[3] Similarly, the USP categorizes compounding into 2 types: sterile preparations and nonsterile preparations (in USP 797 and USP 795, respectively).[4] The definition of compounding under USP 795 specifies that compounds are prepared pursuant to a prescription or medication order. In contrast, USP 797 does not include the term *compounding* in the definitions section but does differentiate between sterile and nonsterile compounding. The lack of a universal definition of compounding highlights how compounding practices need to be more clearly defined and regulated.

TABLE 1 Compounding Definitions[1,3,4]

Organization	Definition	Publication
FDA	"The term 'compounding' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling"	Section 503A of the FD&C Act
	"The term 'compounding' includes the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug"	Section 503B of the FD&C Act
USP	"The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient pharmacist/compounder relationship in the course of professional practice"	Chapter 795, Pharmaceutical Compounding—Nonsterile Preparations
	"Sterile compounding differs from nonsterile compounding…primarily by requiring the maintenance of sterility when compounding exclusively with sterile ingredients and components (i.e., with immediate-use CSPs, low-risk level CSPs, and medium-risk level CSPs) and the achievement of sterility when compounding with nonsterile ingredients and components (i.e., with high-risk level CSPs)"	Chapter 797, Pharmaceutical Compounding—Sterile Preparations

CSPs = compounded sterile preparations; FDA = U.S. Food and Drug Administration; FD&C Act = Food, Drug, and Cosmetic Act; USP = United States Pharmacopeial Convention.

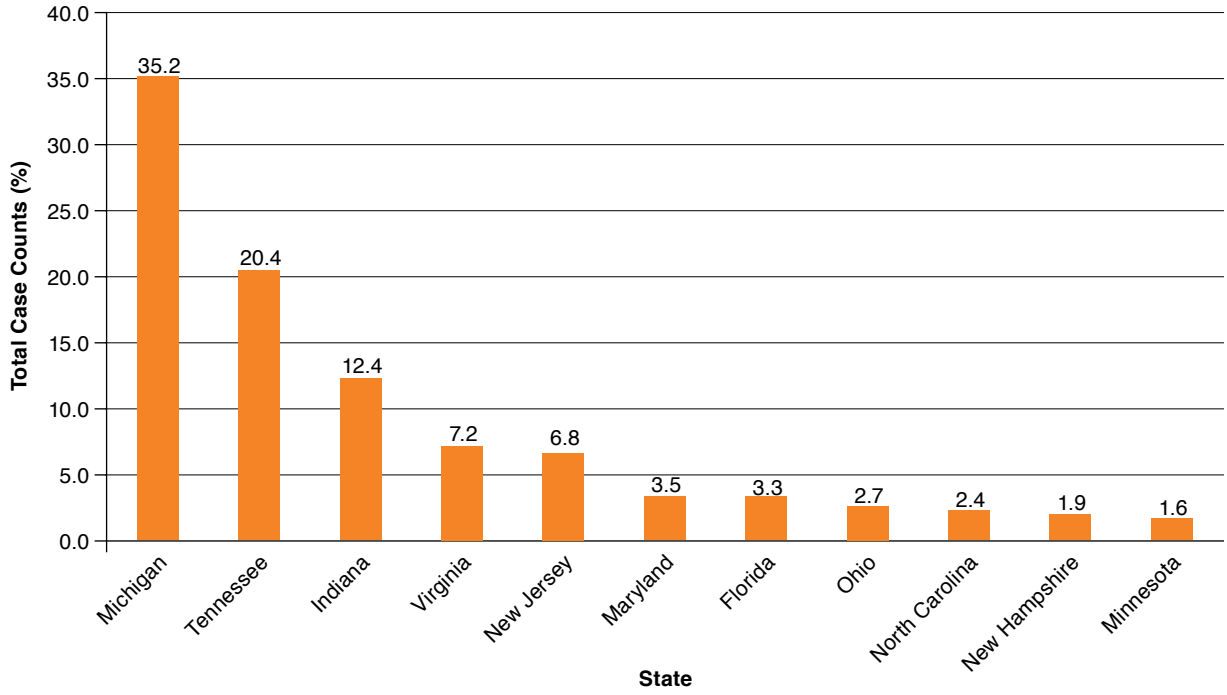
FIGURE 1 Summary of Search and Selection Process



According to the FDA, manufacturing is defined as "all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer."[5] USP has a similar definition: "The production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis. Manufacturing may also include any packaging or repackaging of the substance(s) or labeling or relabeling of containers for resale by pharmacies, practitioners, or other persons."[4] Less ambiguity surrounding manufacturing practices exists compared with compounding—again supporting that compounding practices need to be more clearly defined and regulated.

In the United States, pharmacy compounding has traditionally been regulated by state boards of pharmacy rather than the FDA. State boards of pharmacy recognize the intent of compounding as making a medicinal treatment secondary to a prescription written for a specific patient.[6] Traditionally, the role of compounding has been for a licensed pharmacist or physician to combine, mix, and alter ingredients to create unique medications for patients in response to a prescription.[6] These patients may have a drug allergy to a specific ingredient, or a child may require a liquid dosage form.[7] However, there are some pharmacies that are producing compounds in bulk quantities, not for specific patients in response to a prescription, and distributing across state lines to health systems,

FIGURE 2 Fungal Infections Linked to Steroid Injections (Total Case Counts Across the United States)[2]



Note: Georgia, Idaho, Illinois, New York, Pennsylvania, Rhode Island, South Carolina, Texas, and West Virginia each had less than 1%.

hospitals, and clinics. Such practice is considered manufacturing and, therefore, should fall under the regulatory authority of the FDA instead of the state.[8]

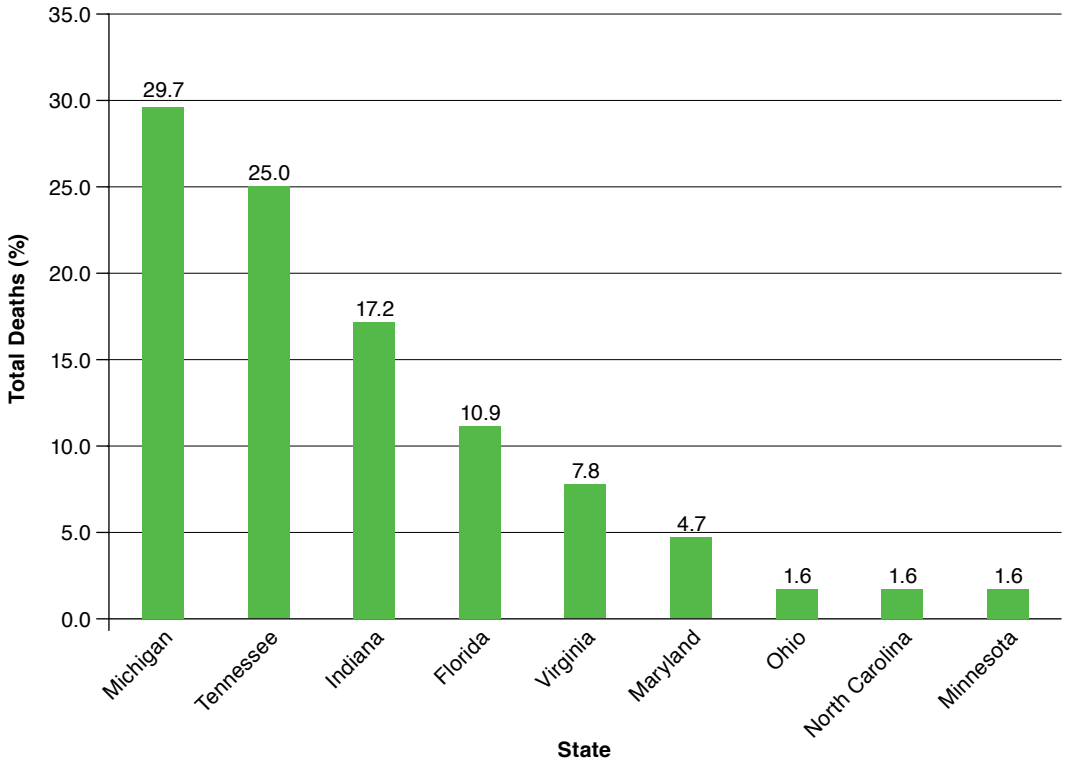
Compounded products generally do not have studies regarding stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy, or safety.[9-12] The 2012-2013 fungal infections outbreak underscored concerns regarding lack of compound safety data, and the Drug Quality and Security Act (DQSA) was signed into law November 27, 2013, to improve regulation of compounding pharmacies.[13] The DQSA created a new class of manufacturers known as "outsourcing facilities," for compounders that voluntarily register with the FDA under section 503B of the FD&C Act. Standards were also established to track pharmaceutical products throughout the distribution chain. Despite these regulatory and legal advancements, there are still gaps in oversight that place patients at risk for infections and other adverse events. Therefore, managed care organizations (MCOs) have many factors to consider when determining how to best manage the safety risks associated with pharmacy compounds.

The purpose of this article was to review the clinical, legal, and regulatory implications of pharmacy compounding for patient safety related to the fungal infections outbreak of 2012-2013 and to discuss strategies MCOs can use to promote safe compounding practices.

Methods

A comprehensive PubMed search was conducted for the time period October 2012 through March 2014 using the search terms "drug compounding and fungal infection" and "fungal meningitis outbreak" (Figure 1). The literature search was focused on a specific time period to capture articles on the 2012-2013 fungal infections outbreak and prevent overlap with other review papers published to date. Additional information related to drug compounding, the FD&C Act, and the DQSA was obtained from the FDA website. Titles and abstracts were screened to identify studies that met the following inclusion criteria: (a) review of pharmacy compounding practices, (b) description of infections and other outbreaks occurring as a result of compounding, (c) review of regulatory or legal framework involved in pharmacy compounding, (d) costs associated with compounding, and (e) managed care approach to managing compounds. Subsequent to an initial screening of the articles, all authors reviewed the objectives and methods sections of identified articles to ensure that all publications were consistent with the screening criteria. Variables of assessment included (a) specific descriptions of clinical, legal, and regulatory problems in pharmacy compounding; (b) clinical recommendations for improving pharmacy compounding; (c) legal recommendations for pharmacy compounding; (d) regulatory recommendations for pharmacy compounding; and (e) economic costs of

FIGURE 3 Deaths Due to Contaminated Steroid Injections[2]



Note: Georgia, Idaho, Illinois, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, South Carolina, Texas, and West Virginia had less than 1%.

pharmacy compounding and compounding accidents. A full review was then conducted to exclude any reviews or studies focusing solely on animals, drug design, or drug discovery. Full reviews of the retrieved publications were completed, examining the clinical, legal, and regulatory implications for pharmacy compounding, as well as any benefits or risks that were described relating to pharmacy compounding. Reference lists of publications were manually examined to capture any publications not identified through the electronic search.

Results

As shown in Figures 2 and 3, Michigan had the most confirmed cases (264/751 [35.2%]) and deaths (19/64 [29.7%]), followed by Tennessee with 153 (20.4%) and 16 (25.0%), respectively.[2] Table 2 displays the characteristics of each study included in this review. The literature review yielded 4 published reports that were original articles. Several articles were excluded due to multiple reports of the same data (n = 18), commentary/editorial (n = 13), news article (n = 11), and review article (n = 9). Other reasons for exclusion are included in Figure 1.

Clinical Implications

The NECC fungal infections outbreak is the largest outbreak of health care-associated infections in the United States. A total of 13,534 individuals were potentially exposed, based on an active review of records by clinical facilities and state and local health departments. Epidural, spinal, or paraspinal injections accounted for 89.0% (12,068) of exposures, and 12.0% (1,648) of the exposures were attributed to peripheral-joint or other injections.[14] Three lots of compounded preservative-free methylprednisolone acetate (05212012@68, 06292012@26, or 08102012@51) were responsible for the outbreak and comprised 17,675 vials distributed to 76 facilities across 23 states.[14,15]

Chart reviews of emergency room and inpatient medical records were conducted between October 1 and November 19, 2012, among the 6 states (Florida, Indiana, Michigan, New Jersey, Tennessee, and Virginia) with the most cases of fungal infections caused by methylprednisolone injections.[16] Among the 328 patients evaluated, disease types ranged from very mild to life threatening, demonstrating that clinical disease spanned a wide spectrum. The majority of patients (265 [81.0%]) had central nervous system (CNS) infections, and a smaller proportion (63 [19.0%]) were diagnosed with non-CNS infections (Table 3). Patients with CNS infections received an injection in states other than Michigan ($P < 0.001$), had a cumulative dose of methylprednisolone acetate 80 milligrams or higher ($P = 0.04$), received a translaminar epidural injection ($P < 0.001$), and had

TABLE 2 Study Characteristics

Study	Number of Patients	Setting	Data Sources
Smith et al. (2013)[14]	728	20 states that submitted information to the CDC as of July 1, 2013	Standardized case-report forms from clinical facilities and state and local health departments
Kainer et al. (2012)[15]	66	Tennessee	Medical chart reviews and interviews with patients, their families, and physicians from 3 Tennessee clinics that received methylprednisolone from NECC
Chiller et al. (2013)[16]	328	Florida, Indiana, Michigan, New Jersey, Tennessee, and Virginia (top 6 states with the most reported cases)	Single review of emergency room and inpatient medical records
Pettit et al. (2012)[18]	1	Tennessee	Inpatient medical records

CDC = Centers for Disease Control and Prevention; NECC = New England Compounding Center.

diabetes ($P = 0.02$) or hypertension ($P = 0.05$), compared with patients with non-CNS infections.[16] Among patients with non-CNS infections alone, 57 (90.0%) received their injections in Michigan.

Overall, the median incubation period (from time of last injection to initial diagnosis) was 47 days, ranging from 0 to 249 days.[14] The fact that some diagnoses were made more than 8 months after the last injection reflects the subacute nature of fungal infections related to the CNS.[14] Patients with peripheral-joint infections had the longest incubation period, with a median 65 days ranging from 22 to 190 days. Incubation period was shortest among patients with stroke without meningitis, median of 24 days ranging from 3 to 157 days.[14] Typically, infections occurring from epidural or paraspinal injections occur in <0.1% of patients. If infection was to result, the type of infection would usually be bacterial, not fungal.[17] The isolated organism from the index case was *Aspergillus fumigatus*, a rare fungus among immunocompetent patients.[18-20] *Exserohilum rostratum* was the predominant fungus of the NECC fungal infections outbreak and is an extremely rare human pathogen.[16]

The lack of quality control at NECC highlights how complications, including those that are fatal, can occur due to poor compounding practices. Because of the subacute nature of some complications, many patients may not be diagnosed for several months. Since most infections occurred approximately 2 months after injection, notification of potentially exposed patients and providers was an appropriate clinical approach because this enabled diagnosing asymptomatic but infected patients earlier in their diseases.

TABLE 3 Disease Types Resulting from Contaminated Methylprednisolone Acetate Injections Among the Top 6 States Impacted, N = 328[16]

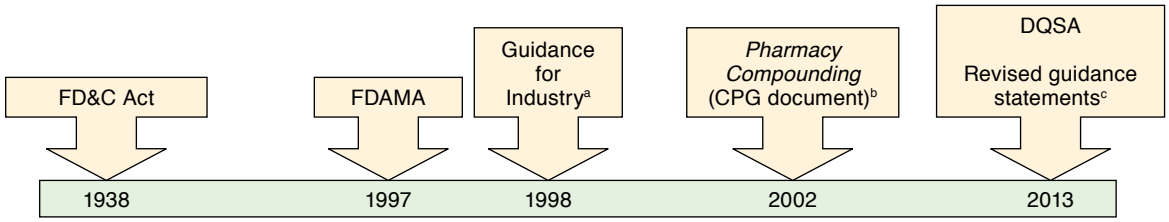
Diagnosis[a]	n	(%)
CNS		
Meningitis	250	(76.2)
Arachnoiditis	63	(19.2)
Stroke	35	(10.7)
Intradural abcess	3	(0.9)
Non-CNS		
Epidural abcess	90	(27.4)
Nonspecific enhancement on spinal imaging	47	(14.3)
Spinal osteomyelitis or diskitis	21	(6.4)
Paraspinal or facet-joint infection	18	(5.5)

[a]Of 328 patients, 122 (37%) were included in multiple categories, since they had more than 1 diagnosis.
CNS = central nervous system.

Legal and Regulatory Implications

Historically, pharmacy compounding has been inadequately regulated. Past federal rulings were inconsistent regarding section 503A, which was added to the FD&C Act by the Food and Drug Administration Modernization Act (FDAMA) of 1997. In November 1998, the FDA issued a guidance for industry entitled *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act*.[21] Section 503A exempts compounded drugs from the following manufacturer requirements: current good manufacturing practices (CGMPs), labeling with adequate directions for use, and FDA approval under new drug applications (NDAs) or abbreviated new drug applications (ANDAs).[1,21] However, section 503A specifically prohibited the advertising and promotion of compounded drugs, practices typically employed by drug manufacturers to gain market share. Since the intent of drug compounding is creating medicinal treatments for individual patients' needs, a drug compounder has minimal need to advertise its drug products.[22] Section 503A also prohibited the solicitation of prescriptions for a compounded drug product.[21] In 2001, compounding pharmacies challenged the advertising and promotion limitations of section 503A based on infringement of freedom of speech rights granted by the First Amendment to the U.S. Constitution.[22,23] The 9th Circuit Court of Appeals ruled in favor of the compounding pharmacies, concluding that the advertising and promotion limitations of 503A are unconstitutional. The advertising and promotion sections were deemed inseparable from the rest of section 503A, rendering the entire section invalid and unenforceable by the FDA.[22] Thus, compounded drugs were now considered "new drugs" that must undergo FDA approval through NDAs or ANDAs. The FDA consequently released the 2002 compliance policy guide (CPG) entitled *Pharmacy Compounding*. This guidance differentiated manufacturing from compounding but still upheld that

FIGURE 4 Timeline of Compounding Guidance Documents



[a]*Document entitled "Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act."*

[b]*The 2002 compliance policy guide.*

[c]*The 2002 compliance policy guide "Pharmacy Compounding" was invalidated by the issuing of 3 new guidance documents addressing compounding: (1) "Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act"; (2) "Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act"; and (3) "Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act."*

DQSA = Drug Quality and Security Act signed on November 27, 2013; FD&C Act = Federal Food, Drug, and Cosmetic Act; FDAMA = Food and Drug Administration Modernization Act of 1997.

compounded drugs were considered "new drugs" requiring FDA approval. In Texas, compounding pharmacies challenged the classification of compounded drugs as "new drugs," leading the 5th Circuit Court of Appeals to revisit the 9th Circuit Court's decision regarding severability of advertising and promotion from the rest of section 503A. The 5th Circuit Court concluded that advertising and promotion could be separated from the rest of section 503A. Such decisions lead to inconsistencies between the federal courts and the FDA over pharmacy compounding.[23] Compounding pharmacies in the 9th Circuit were accountable to the CPG *Pharmacy Compounding* guidelines, while compounders in the 5th Circuit were accountable to section 503A. The timeline of events with respect to compounding guidance documents are illustrated in Figure 4.

A rise in infectious outbreaks highlighted regulatory gaps, increasing pressure for more regulation over compounding. As a result, the DQSA was passed and signed into law on November 27, 2013.[12] The DQSA created a new section in the FD&C Act, section 503B outsourcing facilities, that addresses sterile compounding. Section 503B removed the advertising and promotion provisions from section 503A, since they were ruled unconstitutional. This action eliminated ambiguity surrounding section 503A's validity, affirming that section 503A applies universally throughout the United States.[1] With the passing of the DQSA in November 2013, the FDA withdrew the 2002 CPG *Pharmacy Compounding* guidelines and the 1998 guidance for Section 503A.[3,21] In December 2013, the FDA released 3 guidance documents addressing its updated position on compounding: (1) *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act;* (2) *Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act;* and (3) *Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.*[19,23,24]

Table 4 summarizes key features of traditional compounding versus sterile compounding. Prior to 2013, the FDA had not issued a guidance that specifically addressed sterile compounding. According to section 503B, a sterile drug is a "drug that is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law."[1] Outsourcing facilities must meet the following: (a) CGMP requirements; (b) FDA inspections if considered high risk; and (c) reporting requirements, including adverse events and specific product information.[1] CGMP requirements involve processes and quality assurances to ensure superior products.[25] Risk factors that merit FDA inspection of a particular outsourcing facility include the following: compliance history; record, history, and nature of recalls; inherent risk of compounded drug products; inspection frequency and history; intent to compound drugs appearing on FDA's drug shortage list; and any other criteria deemed necessary and appropriate.[1] The reporting of adverse events by an outsourcing facility is similar to requirements that manufacturers follow. Product information that will be collected from outsourcing facilities include product name and National Drug Code (NDC) number, ingredient name and strength, dosage form, route of administration, a package description, and number of units.[26]

Registration with the FDA as an outsourcing facility is voluntary, with a registration fee required as of October 1, 2014.[24] Facilities must register annually between October 1 and December 31 of each year.[23] As of February 28, 2014 (approximately 3 months after the DQSA's passing),[27] a total of 28 outsourcing facilities were registered with the FDA. In December 2013, the agency had estimated that approximately 700-1,000 facilities could potentially qualify as an outsourcing facility.

Secondary to the NECC fungal infections outbreak, compounding recalls have been receiving more attention. During March through December 2013, a total of 30 recalls regarding

TABLE 4 Traditional Compounding Versus Sterile Compounding[1,3,21,24]

Key Features	Traditional Compounding	Sterile Compounding
Regulatory publication	Section 503A of FD&C Act	Section 503B of FD&C Act
Predominant regulatory body with authority	State boards of pharmacy	FDA
Type of facilities	Pharmacies engaging in the practice of compounding that do not register with the FDA as an outsourcing facility	Pharmacies that voluntarily register with the FDA as an outsourcing facility[a]
Exemptions	1. Compliance with CGMPs 2. Labeling with adequate directions for use 3. FDA approval through NDAs or ANDAs	1. Labeling with adequate directions for use 2. FDA approval through NDAs or ANDAs Note: Compliance with CGMPs does apply to outsourcing facilities
Prescription required for an individual patient?	Yes	No

[a]*An outsourcing facility is engaged in the compounding of sterile drugs and complies with all requirements under section 503B of the Food, Drug, and Cosmetic Act.*
ANDAs = abbreviated new drug applications; CGMPs = current good manufacturing processes; FD&C Act = Food, Drug, and Cosmetic Act; FDA = U.S. Food and Drug Administration; NDAs = new drug applications.

compounded products were issued by pharmacies. A large proportion (23/30 [76.7%]) were recalls for all sterile products from specific facilities. Recalls were attributed to lack of sterility assurance, reports of adverse events, and quality control concerns.[28]

Discussion

MCOs have many factors to consider regarding management of compounded drug products. These factors include safety and efficacy supporting use for a specific indication, ingredients, quality assurance, qualifications of the pharmacy such as registration with the FDA, and cost of bulk ingredients.

Compounded drugs are not subject to the drug approval process; therefore, safety and efficacy has not been reviewed by the FDA and product quality cannot be guaranteed.[11,12] When MCOs reimburse manufactured products, there is a level of confidence in the FDA's review process. Since compounded products are not subject to FDA's review through an NDA or ANDA, many health plans require a clinical review for coverage determination of compounded medications. MCOs consider the medical necessity of the compounded product and the accessibility of commercially available alternatives. The FDA recommends that compounded drugs should only be used in patients if an FDA-approved product is unavailable to meet the medical needs of a patient.[7,11,12] MCOs may require prior authorization for compounded products, which would consider criteria such as medical necessity or access to commercially available products and ingredients.

Sections 503A and 503B require the FDA to develop lists of drugs and bulk drug substances that are permissible and nonpermissible as ingredients in compounded products (Table 5). MCOs can leverage such lists in determining coverage of compounded products. Under section 503A, a bulk drug substance is permissible only if the substance complies with standards of a USP or National Formulary (NF) monograph. If a USP or NF monograph does not exist, then the bulk drug substance must be a component of an FDA-approved human drug product or included on a list of bulk drug substances permissible by the FDA (Table 5). Likewise, section 503B states that if a USP, NF, or comparable compendium does not exist for a bulk drug substance, the substance must be included on the FDA's list of bulk drug substances that meets clinical needs in order to be permissible. Section 503B also allows bulk drug substances in compounds if included on the FDA's drug shortage list.[1,29]

MCOs can promote use of quality compounded drugs by contracting with specific compounding pharmacies and allowing payment only to these providers for compounded sterile products. On January 8, 2014, FDA Commissioner Margaret Hamburg sent letters to stakeholders, including hospitals, purchasers, and state officials, encouraging purchasers of compounded drugs to require registration of compounding pharmacies as outsourcing facilities.[11,12] The FDA will enforce the following for outsourcing facilities: inspections on a risk-based schedule, CGMP requirements, adverse event reporting, and appropriate labeling.[11-13] MCOs can help ensure that compounded products are safe by contracting with and reimbursing for compounds only from registered outsourcing facilities.

Outsourcing facilities must biannually report all drugs compounded in the previous 6-month period; therefore, the FDA will know exactly what outsourcing facilities are compounding. Required biannual reporting includes active ingredient, strength of active ingredient per unit, source of active ingredient (bulk or finished drug), NDC number, dosage form, route of administration, package description, number of individual units produced, and NDC number of final product.[13,26] Increased reporting requirements such as biannual reporting will provide a mechanism for greater pharmacy compounding oversight, which may reduce pharmaceutical fraud as well as adverse events associated with compounding.

Alternatively, MCOs may evaluate compounding pharmacies using a selection tool known as the Compounding Pharmacy Assessment Questionnaire (CPAQ) or requiring accreditation by the Pharmacy Compounding Accreditation Board (PCAB).[30,31] Based on USP standards, the CPAQ is a tool that can be utilized by pharmacies for self-assessment

TABLE 5 FDA Drug Lists Related to Compounding[1,3,29,34,35]

Permissible
Bulk Drug Substances that May be Used to Compound Drug Products in Accordance with Section 503A of the FD&C Act[a]
Bulk Drug Substances that May be Used to Compound Drug Products in Accordance with Section 503B of the FD&C Act Concerning Outsourcing Facilities[a]
FDA Drug Shortage List
Nonpermissible
Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the FD&C Act[a]
List of Drug Products that Have Been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness

[a]Requests for nominations ended September 30, 2014. Final list not released as of August 10, 2014.[36,37]

FD&C Act = Food, Drug, and Cosmetic Act; FDA = U.S. Food and Drug Administration.

or by MCOs wanting to formally evaluate practice quality at a compounding pharmacy. The CPAQ evaluates compounding pharmacies in the following areas: (a) regulatory compliance; (b) licensing, including permits, internal controls, and quality assurance; and (c) testing and verification, including stability, quality assurance and improvement, training, air quality, and whether or not USP standards are met.[32] The CPAQ also assesses whether or not the compounding pharmacy is able to accommodate a site visit.[32] PCAB accreditation is voluntary and includes the following quality standards: use of high-quality chemicals and equipment; regular, specialized training of pharmacists and pharmacy technicians; system of testing to evaluate quality of products; and tracking mechanism to identify who receives particular compounds.[33] Pharmacies can obtain PCAB accreditation by filing an application, paying registration and accreditation fees, and meeting the standards for pharmacies set by the state in which they are located.[33] MCOs may also require certification of all pharmacy technicians and documentation of training provided to staff. On-site audits may also provide assurances to MCOs that compounding practices are appropriate.

Limitations

All reviewed publications were identified by 1 search engine. The authors believe results from the PubMed search engine are representative of information in this field. However, few randomized controlled trials are published in the field of pharmacy compounding; therefore, references included in this review are primarily case reports/series identified via PubMed as well as FDA documents. Additionally, some inherent risks of drug compounding are not easily studied or accounted for. This review did not address risks such as human error or gross errors associated with adding excipients in the compounding process. Quality control and regulatory efforts do not always adequately address such risks. Given the paucity of randomized controlled trials regarding safety and efficacy of pharmacy compounding, and focusing the literature search on the 2012-2013 fungal infections outbreak, there is a risk for publication and retrieval bias.

Conclusions

The DQSA marks an important milestone in improving drug compounding practices. Pharmacy compounding has significant safety risks with limited evidence of efficacy, an imbalance that can jeopardize patient safety. The impact of DQSA will unfold with time, and the U.S. Government Accountability Office is expected to release a report addressing the status of drug compounding practices in the United States within 36 months of the DQSA's enactment. Since registration is voluntary and not required of compounders producing sterile compounds, uncertainty still remains regarding advancement in safe compounding practices. Regardless, MCOs can employ multiple strategies to help ensure patient safety and promote appropriate drug therapy.

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DISCLOSURES

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