

History of sterile compounding in U.S. hospitals: Learning from the tragic lessons of the past

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After yet another widely publicized tragedy related to microbial contamination of compounded injections,¹ there is value in reviewing the long history of problems associated with sterile compounded medicines in the United States. The ultimate elimination of these problems must be built on an understanding of how we arrived at the situation we are in today. The purpose of this paper is to aid that understanding by reviewing, in the context of hospital patient care, how the technology associated with injections has evolved, the major previous incidents of morbidity and mortality associated with compounded sterile medicines, and the efforts made over the years to improve compounding practices. In addition, several ideas are offered for helping address this seemingly intractable issue.

The exact prevalence of compounding in general is not known.²⁻⁶ It is estimated that 60% of the medications dispensed in pharmacies in the 1930s and 1940s in the United States were compounded.² An analysis in 2006 estimated that compounding (mostly nonsterile) occurred in fewer than 1% of com-

Purpose. The evolution of sterile compounding in the context of hospital patient care, the evolution of related technology, past incidents of morbidity and mortality associated with preparations compounded in various settings, and efforts over the years to improve compounding practices are reviewed.

Summary. Tightened United States Pharmacopeial Convention standards (since 2004) for sterile compounding made it difficult for hospitals to achieve all of the sterile compounding necessary for patient care. Shortages of manufactured injections added to the need for compounding. Non-hospital-based compounding pharmacies increased sterile compounding to meet the needs. Gaps in federal and state laws and regulations about compounding pharmacies led to deficiencies in their regulation. Lapses in sterility led to injuries and deaths. Perspectives offered include potential actions, including changes in practitioner education, better surveillance of sterile compounding, regulatory reforms, reexamination of the causes of drug shortages, and the development of new technologies.

Conclusion. Over the years, there have been numerous exhortations for voluntary better performance in sterile compounding. In addition, professional leadership has been vigorous and extensive in the form of guidance, publications, education, enforceable standards, and development of various associations and organizations dealing with safe compounding practices. Yet problems continue to occur. We must engage in diligent learning from the injuries and tragedies that have occurred. Assuming that we are already doing all we can to avoid problems would be an abdication of the professional mission of pharmacists. It would be wrong thinking to assume that the recent problems in large-scale compounding pharmacies are the only problems that warrant attention. It is time for a systematic assessment of the nature and the dimensions of the problems in every type of setting where sterile compounding occurs. It also is time for some innovative thinking about ensuring safety in sterile compounding.

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munity pharmacies.⁶ In numbers attributed to the president of the International Academy of Compounding Pharmacies (IACP), there were 5000 compounding pharmacies in 2009

and 7500 in 2012.⁵ (The number in the United States was not stated.) How many of these specialized in compounding as their predominant activity is unknown.

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Most of the history of sterile compounding evolved in hospitals, where customized injections—many of them i.v. injections—are necessary for patient care. Some sterile ophthalmic and inhalation preparations are compounded as well.

Milestones in the technology of i.v. therapy

Injections were uncommon into the mid-1920s. In 1926, the *Pharmacopoeia of the United States* included only two injections, both of which were included for the first time.⁷ In the same year, *The National Formulary* listed injections for the first time; only 7 were listed.⁸ Most of the sterile medications used in hospitals and other health systems (e.g., home infusion) today are injections. Most of the injections compounded in those settings are large-volume i.v. solutions (LVISs) and small-volume injections (SVIs; for example, medications in vials, syringes, and secondary infusion containers).⁹ Most of the compounded items are prepared by aseptic dilution, mixing, or repackaging of sterile injections that were made by licensed manufacturers under the regulatory scrutiny of the Food and Drug Administration (FDA). Since the components used in aseptic compounding are already sterile, typically a final sterilization of the compounded preparations does not occur. The 2013 edition of the *Handbook on Injectable Drugs* covers 332 injections.¹¹ In 2010, FDA reported 569 approved injection molecules, all of which may have been manufactured in various concentrations and volumes.¹² The 2013 edition of the *United States Pharmacopoeia* listed 566 injections.⁹

Until 1933, hospitals in the United States made their own LVISs. In that year, the first manufactured sterile LVISs became available.¹³ In 1955, the U.S. Public Health Service funded an audit of pharmacy services in U.S. hospitals. The American Society of Hospital Pharmacists (now the

American Society of Health-System Pharmacists [ASHP]) published the report of the audit as *Mirror to Hospital Pharmacy* in 1964.¹⁴ The report documented major deficiencies in sterile preparation, including the facts that (1) central sterile service (CSS) departments made LVISs in 58% of hospitals (pharmacy made them in 39%), (2) CSSs made SVIs in 22% of hospitals (pharmacy made them in 71%), and (3) CSSs made sterile surgical irrigation solutions in 48% of hospitals (pharmacy made them in 37%). That audit inspired ASHP's recurring surveys of hospital pharmacy practice that have regularly occurred since the 1955 audit.¹⁵⁻³¹ (There were many more surveys; listed in these references are only those that dealt with sterile preparations.) In 1961, 90% of hospitals made their own sterile surgical irrigation solutions.³²

As early as the 1940s, hospital pharmacists expressed a need for improvements in hospital medication handling, including injections.^{33,34} In the early to mid-1960s, they more strongly urged centralized pharmacy handling of all medications, including injections.³⁵⁻³⁷ That evolved over time, but a challenging changeover was the handling of i.v. admixtures (the adding of an injection to an LVIS or SVI). In the early 1960s, this task was largely carried out by nurses in patient care areas. By the 1950s, it was common after surgery for nurses to add potassium chloride and vitamins B and C to LVISs.¹³ With the development of chemical laboratory analyses for blood electrolytes after 1950, the prescribing of i.v. additives increased substantially. Pharmacists also had long expressed concerns about incompatibilities in the use of injections³⁸; they reiterated those concerns in 1966.³⁹ Drug additives were present in 70% of one hospital's LVISs administered in 1966 and in 86% in another hospital in 1968.^{40,41} By 1981, 60% of hospitalized patients received an LVIS; two thirds of those included a drug additive.⁴²

Hospital pharmacists documented recommended facilities and procedures for sterile preparation in 1961 and 1962.⁴³⁻⁴⁶ Pharmacy-based i.v. admixture services began at the Clinical Center of the National Institutes of Health in 1963 (Gallelli JF, Pierpaoli PG, personal communications, 2013 Apr 1 and 5). An i.v. admixture service was implemented in a hospital pharmacy in a teaching hospital in 1965.⁴⁷ Over time, hospital pharmacists achieved a steady expansion of centralized i.v. admixture services.¹⁵⁻³¹ In 1962, cephalothin injection was introduced.⁴⁸ It was frequently prescribed to be administered intravenously because it was painful when administered intramuscularly. However, even during i.v. administration, if it was administered too fast (which introduced a high concentration of the drug at and near the venipuncture site) or if it was administered for a prolonged duration, patients experienced significant phlebitis. By the 1970s, Y-site-attached sterile plastic chambers (e.g., Buretrol, Soluset, Volutrol) were devised to enable intermittent addition of such drugs in conjunction with an LVIS.^{49,50} The chambers later evolved to separate secondary infusion containers—"minibottles" and "minibags" ("piggybacks"). The latter became commonly prepared in centralized pharmacy i.v. admixture services. Stability concerns led to successful freezing of admixed i.v. fluids. Additional challenges occurred with the admixing of antineoplastic injections, whose doses and combinations were customized to specific patients. This lack of standardization added to the complexity of i.v. admixture services (Godwin HN, personal communication, 2013 Jan 21).

Concurrent with the emergence of centralized i.v. admixture services in the early to mid-1960s, laminar-airflow rooms and hoods using high-efficiency particulate air (HEPA) filters were first implemented.⁵¹⁻⁵⁴ In the absence of laminar-airflow

hoods, the Clinical Center of the National Institutes of Health used an ultraviolet cabinet in conjunction with its first i.v. admixture services in 1963 (Gallelli JF, Pierpaoli PG, personal communications, 2013 Apr 2 and 5). The first known use of laminar-airflow hoods in a hospital pharmacy occurred in 1964 in an experimental unit-dose drug distribution system at the University of Arkansas Medical Center Hospital (an experiment supported by a grant from the U.S. Public Health Service) (Heller WM, Barker KN, personal communications, 2013 Jan 20).⁵¹ Laminar-airflow hoods, however, were expensive and required a significant commitment of floor or counter workspace. Training had to occur in order for workers to use them, and periodic recertification of the equipment was required. These factors made their hospitalwide installation on all nursing units unachievable. They were highly desired in hospital pharmacies for use in centralized i.v. admixture services, but (because of the same limiting factors) their acquisition and implementation were protracted even there. Additional deterrents to the expansion of centralized i.v. admixture services were the lack of rapid medication-order communication mechanisms (among prescribers, pharmacists, and nurses) and a lack of rapid product-transport mechanisms within most hospitals. Transferring i.v. admixing from nursing staff to pharmacy staff did not reduce nurse staff levels, but it added to pharmacy staff levels, which was an economic challenge for hospitals.

Microbes capable of becoming human pathogens are ubiquitous. In and on the human body there are 150–200 classes of bacteria, which do not include other microbes such as viruses and fungi.⁵⁵ Workers' hands have approximately 100,000 organisms per square millimeter. Approximately 5 g of skin particles are released per day, all of which can serve as “dust” capable of acting as

vectors for bacteria. Clothing particles can do so as well. In a study of a workroom intended to have no more than 100,000 particles per cubic foot, the air was found to contain approximately 36,000 particles greater than 0.5 μm in size per cubic foot.⁵⁶ The established standard in 2004 and still today for even the lowest risk level of sterile compounding is that the work environment air should contain no more than 100 of such particles per cubic foot.⁵⁷ There are more than 10 million particles (0.3 μm or larger) on 1 sq ft of the cleanest hands.⁵⁸ The principal aim and the state of the art in most of the lowest-level sterile compounding in hospitals and home infusion today are to preclude the entry of particles and microbes into already-sterile manufactured ingredients while they are being manipulated and mixed. Thanks to the ingenuity of W. J. Whitfield,^{52,53} who worked in the microelectronics industry and who invented laminar airflow using HEPA filtration, much cleaner compounding work environments were made possible. A typical laminar-airflow hood directs HEPA-filtered air from a far wall in the hood toward a worker who is located across the work area and facing the airflow. When it is necessary to compound medications that are hazardous to workers, the configuration is modified so that the airflow moves down from the “ceiling” of the hood rather than toward the worker. Whitfield's inventions likely have prevented uncountable infections related to sterile compounding.⁵⁹

In 1967, the first successful human parenteral nutrition procedure occurred.⁶⁰ This launched a substantial change in sterile compounding in hospitals. Compounding a parenteral nutrition fluid went well beyond adding a small volume of an injection to an LVIS or a secondary infusion container. It required the mixing of large volumes of highly concentrated ingredients that were only briefly stable. Patients also needed numerous additional i.v. nutrition

support ingredients, including trace elements. Parenteral nutrition formulations commonly required 18 or more ingredients, each of which required aseptic addition. The increased number of manipulations generated many more opportunities for contamination, and the increased number of ingredients required a very careful sequencing of additives to avoid precipitates. In 1975, a lipid emulsion product (Intralipid) was introduced for parenteral nutrition.^{61,62} This was a therapeutic advance in that it provided a way to administer high calories without the accompanying need for large volumes of fluid. However, it also added to the complexity of sterile compounding in hospital pharmacies. Emulsions are fragile chemical forms, and they can be caused to separate into unmixed lipid and water layers by the addition of certain additives and by the sequence of the additions.

A positive development in the 1970s was the development of the Limulus amoebocyte lysate test for pyrogens, which eliminated the need for testing preparations in live rabbits.⁶³ Another advance, in 1971, was the invention of the Millex inline membrane filter that could be attached to a syringe.⁶⁴ This improved the probability that additives could be added without contamination. A documented use of an inline filter for i.v. fluids occurred in 1969.⁶⁵ By 1973, inline filtration of particulates was common in i.v. administration.⁶⁶ Foreign particulates in i.v. solutions were noted as having inflammatory potential in 1977.⁶⁷

A medical–surgical advance that originated in the 1960s became more common in the 1980s: open heart surgery using cardioplegia (immobilization of the heart during surgery by temperature and chemical means).⁶⁸ A manufactured cardioplegia solution did not become available until 2000.⁶⁹ Until then, cardioplegia solutions (which had various formulations) had to be compounded.

Before 1991, automated compounding devices existed to assist in the mixing of dextrose and amino acid solutions for parenteral nutrition. In that year, they were improved to enable automated admixing of small volumes of injections as well, which made it more possible to customize parenteral nutrition formulations for specific patients.^{70,71} These devices also introduced the potential, however, for more errors and led to cautions about quality controls to ensure their performance and accuracy.^{72,73} Eventually the devices were used for admixing solutions other than for parenteral nutrition. Since the devices enabled the addition of numerous ingredients at one time, they required fewer admixture manipulations.⁷³

In the evolution of injection therapy in hospitals, other technology also played a crucial role. The autoclave was invented in 1879.⁷⁴ Without it, the making of sterile LVISs, sterile SVIs, and sterile surgical irrigation solutions in hospitals would have been impossible. By the 1950s, reused rubber bottle stoppers and reused rubber i.v. administration tubing were replaced by disposable plastic devices.¹³ The first disposable plastic syringes became available in 1955.⁷⁵ Parenteral nutrition was followed by indwelling venous access devices (Hickman and Broviac).^{76,77} In 1971, collapsible plastic LVIS containers were introduced, eliminating the need for air venting of glass containers.^{78,79} Infusion pumps improved the safety of i.v. medication administration, though there were difficulties in their evolution.⁸⁰ By 1999, some pharmacies were using barrier isolators, which in effect exclude workers from the compounding work environment.⁸¹

External factors that influenced the use of injections in hospitals and home infusion

A major development occurred in 1983 whose downstream effect

on sterile compounding was not recognized at the time. Medicare initiated standard reimbursements to hospitals based on prepriced therapies.⁸² This reduced Medicare reimbursements to hospitals. Consequently, hospitals looked for ways to reduce costs for hospital care. Hospital lengths of stay were reduced,⁸³ and ambulatory care services were expanded, including same-day surgery.⁸⁴ Medicare began paying for home administration of parenteral nutrition fluids in 1977.⁸⁵ By 1983, independent home infusion services were well established. Hospitals (especially nonprofit hospitals) faced several barriers in developing home infusion services of their own. Nonprofit hospitals would have had to obtain retail pharmacy licenses, purchase infusion materials at retail prices, and maintain such supplies separate from others. They also faced the potential that they could be perceived as engaging in anticompetitive practices if they influenced their own patients to use hospital-owned home infusion services after discharge. Many hospitals lacked the facilities to expand the volume of sterile compounding that would be necessary for home infusion. Hence, non-hospital-based home infusion services came to predominate. This was important because home infusion services demonstrated that sterile compounding could be accomplished outside of a hospital environment and could serve the needs of patients cared for by multiple prescribers not associated with a single hospital. Later, compounding pharmacies emerged to provide similar services and then became sources of supply (for many compounded sterile preparations) for hospitals.

By 2001, shortages of drug products, especially injections made by generic manufacturers, had become frequent and long lasting. This required hospitals and home infusion pharmacies to increase their compounding to make the sterile prepa-

rations necessary for patient care.^{86,87} Some believe that the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 led (by a complex economic pathway) to reduced margins for manufacturers and led some manufacturers to discontinue some injections, which then aggravated shortages.⁸⁸⁻⁹⁰ Others are less certain about that as an influence and point out that there have been many reasons for shortages.⁹¹⁻⁹⁴ In late 2012, FDA listed 118 drug shortages, 84.7% (100) of which were injections.⁹⁵ On the same date, ASHP's drug shortages website listed 225 shortages, 77% (174) of which were injections or other sterile dosage forms that could be compounded.⁹⁶ Compounding pharmacies became sources of supply for hospitals for many of the injections in short supply.

Morbidity and mortality from contaminated preparations

While there are now good standards from the United States Pharmacopeial Convention (USP) for compounding sterile medications, some morbidity and mortality from contaminated preparations have occurred over time. It is of value to review some of the well-known events with an aim toward making improvements. Importantly, this is an incomplete list. Likely, many contaminated compounded preparations simply have not been recognized, since a contaminant may not grow well in some diluents or may be destroyed by patients' host defenses. The events listed here are among those most publicly known.

In 1971, more than 100 patients nationwide died from septicemias caused by LVISs manufactured by Abbott Laboratories, the supplier of 80% of the LVISs used in the United States at that time.^{97,98} The contamination was traced to a flaw in the manufacturer's glass-bottle screw-cap closure. All of the products were immediately recalled from the mar-

ket. Hospitals nationwide scrambled to find alternative suppliers and to educate their nursing staffs about use of the replacement products. While this was not a compounding event, it significantly increased awareness of the potential consequences of contamination in i.v. therapy.

In 1977, drug-related hospital deaths were documented to occur in 1.2 per 1000 patients, some of them from LVISs.⁹⁹ In 1986, 5 deaths occurred as a result of contaminated cardioplegia solutions¹⁰⁰; the source of the contamination was unclear. In 1988, a death occurred from a cardioplegia solution prepared in a hospital using an automated compounding device.¹⁰¹ In 1990, 4 deaths occurred in a hospital as a result of contaminated cardioplegia solutions prepared in the hospital.¹⁰² Also in 1990, several infections and two cases of blindness resulted from contaminated eye drops prepared in a community pharmacy.¹⁰³ In 1994, injuries and 2 deaths resulted from calcium phosphate precipitates that occurred during parenteral nutrition¹⁰⁴; it was not clear where the preparations were compounded. In 1998, 11 children received a drug or drugs from hospital-contaminated syringes.¹⁰⁵ In 2001, 3 deaths occurred from an injection prepared in a compounding pharmacy.¹⁰⁶ In 2001, 4 infections resulted from a hospital-compounded injection.¹⁰⁷ In 2002, 1 death and 4 infections were linked to injections made in a compounding pharmacy.¹⁰⁸ In 2003, bacteria were found in a compounding-pharmacy-prepared inhalant used by 19,000 patients nationwide.¹⁰⁹ In 2004, 36 infections occurred from injections made in a compounding pharmacy.¹¹⁰ In 2005, multiple infections resulted from the administration of i.v. injections made by a compounding pharmacy.¹¹¹ In that same year, 2 patients were blinded by contaminated injections made by a compounding pharmacy.¹¹² Also in 2005, 4 deaths occurred after exposure to

cardioplegia solutions made by a compounding pharmacy.¹¹³ In 2006, a death occurred from a decimal error in compounding in a hospital pharmacy.¹¹⁴ Also in 2006, a death occurred from an overly concentrated injection used in hospital pharmacy compounding.¹¹⁵ In 2007, 3 deaths resulted from an injection made by a compounding pharmacy.¹¹⁶ In 2011, 16 eye infections were linked to a drug repackaged by a compounding pharmacy.¹¹⁷ Also in 2011, 9 deaths resulted from contaminated parenteral nutrition preparations made by a compounding pharmacy.¹¹⁸ In 2012, 33 fungal eye infections (some with loss of vision) resulted from contaminated preparations made by a compounding pharmacy.¹¹⁹

In 2012, the New England Compounding Center (NECC) in Framingham, Massachusetts, produced and distributed three lots of preservative-free methylprednisolone acetate injection.¹ As of March 25, 2013, these preparations had caused 750 infections and 51 deaths in 20 states (380 cases of meningitis, 7 strokes, 308 paraspinal infections, and 35 peripheral joint infections). Intense medical surveillance of the surviving patients is ongoing.

The lots were found to be contaminated with fungi.¹ FDA and the Centers for Disease Control and Prevention also found bacteria or fungi in NECC-made preservative-free betamethasone injection, preservative-free triamcinolone, and cardioplegia solutions.¹²⁰

Full details, including causative and contributing factors for these events, are not included here, but what can we learn from the information above? Three things stand out. First, microbial contamination can occur in any practice setting and can lead to morbidity and mortality. Second, contamination can occur with various types of preparations, from i.v. to ophthalmic and inhalation, for example. Third, over the past two decades, there have been numer-

ous problems from contaminated preparations made in compounding pharmacies.

Professional responses

The expansion in sterile compounding occurred parallel with pharmacy's maturation as a clinical profession. The expansion happened at a time when schools and colleges of pharmacy experienced their own transformation to a more clinical curriculum. That curricular transformation, which began in the 1970s, happened at a time when non-sterile compounding in pharmacy practice had declined and was seen as less of a priority in curriculum content. When sterile compounding surged in hospitals because of medical and technological advances and a dramatic increase in the number of injections, the curricular priority remained focused on clinical pharmacy. A result was that most pharmacy schools and colleges did not include instruction about sterile compounding sufficient to educate and train hospital pharmacists about sterile compounding during the years when sterile compounding was becoming so necessary. Survey data in 2007 revealed that 96% of schools of pharmacy provided at least some didactic and laboratory instruction about compounding sterile preparations, but the depth of instruction varied greatly.¹²¹

Pharmacists who practiced during the expansion of sterile compounding largely learned the principles and procedures of sterile compounding via postgraduate avenues (courses, continuing education, books, guidelines, and in-the-workplace learning). In the 1970s, the Philadelphia College of Pharmacy and Science, through the efforts of Associate Professor Kenneth Avis, offered a two-week in-residence course in sterile preparation. Later, Avis moved to the University of Tennessee, where a similar course was offered. The course content was more related to

industrial production than extemporaneous compounding. However, pharmacists trained in the courses viewed them as key in their development of knowledge about sterile production—knowledge that they then adapted for sterile compounding (Anderson RD, personal communication, 2013 Jan 19). In the late 1960s and early 1970s, other educational programs were offered at many places in the country with the support of LVIS manufacturers (Godwin HN, personal communication, 2013 Jan 21). ASHP conducted 11 three-day educational “institutes” about i.v. therapy and i.v. admixtures during the 1970s (Callas A, ASHP, personal communication, 2013 Jan 17). The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), founded in 1976,¹²² provided continuing education on the subject of parenteral nutrition. Today, many pharmacists learn about sterile compounding during ASHP-accredited hospital pharmacy residencies.

Pharmacy technicians must be taught as well. ASHP began accrediting pharmacy technician training programs in 1983. Those programs include instruction in sterile compounding,¹²³ but not all pharmacy technicians are graduates of such programs. Moreover, pharmacy has not adopted uniform requirements for the training, certification, and licensure of all pharmacy technicians. National certification of pharmacy technicians by the Pharmacy Technician Certification Board (PTCB) is increasingly being accepted by state regulatory bodies as a desired or required credential.¹²⁴ By 2020, PTCB will require certification candidates to be graduates of an ASHP-accredited pharmacy technician training program before becoming certified.¹²⁵ Currently, there is no advanced certification available from PTCB for sterile compounding nor are there regulatory requirements for specialized training for pharmacy technicians for sterile compounding.

Pharmacists, through their pharmacy degree education, typically receive formal instruction in microbiology. Pharmacy technicians, even those in formal training programs, receive much less. Hence, the training (much of it in the workplace) of pharmacy technicians with respect to sterile compounding has been more skills based than knowledge based.

After the tragedies with Abbott's LVISs in 1971,^{97,98} the U.S. Department of Health and Human Services in 1975 provided a grant to USP to develop recommendations for the production and administration of i.v.'s. From 1975 through 1979, the body assembled to accomplish this—the National Coordinating Committee on Large Volume Parenterals (NCCLVP)—issued numerous recommendations that provided excellent guidance for those engaged in sterile production, compounding, and administration.^{42,126-132} This was the most comprehensive guidance about sterile compounding available at that time for hospital pharmacists. The organizations represented in NCCLVP were the American Association of I.V. Therapy, the American Hospital Association, the American Medical Association, the American Nurses' Association, ASHP, the Centers for Disease Control, FDA, the Joint Commission on Accreditation of Hospitals, the National Association of Boards of Pharmacy, the National Association for Practical Nurse Education and Services, the National Intravenous Therapy Association, the Parenteral Drug Association, USP, and the major manufacturers of large-volume parenterals (Abbott, Cutter, McGaw, and Travenol).⁴²

In 1971 and 1978, the first editions of reference books about i.v. drug incompatibilities and stabilities were published: *King Guide to Parenteral Admixtures* (published independently)¹³³ and the *Handbook on Injectable Drugs* (published by ASHP).¹³⁴ The *Handbook* was preceded by ASHP's publication of the

Parenteral Drug Information Guide in 1974,¹³⁵ a reference based on internal guidance developed at the Clinical Center of the National Institutes of Health.

By 1981, many community pharmacies (mostly independent) were increasing their engagement in compounding. In that year, the Professional Compounding Centers of America was founded to provide to them information and a source for compounding ingredients and equipment.¹³⁶

The early and mid-1990s were important years in hospital and home infusion sterile compounding. The aforementioned deaths of the four patients receiving contaminated cardioplegia solutions in 1990¹⁰² plus (in the same year) the two cases of blindness caused by contaminated eye drops made in a community pharmacy¹⁰³ influenced ASHP to develop a multistep action plan to improve the preparation of sterile medications by pharmacists.¹³⁷ In 1991, ASHP conducted an invitational conference to begin planning further actions.¹³⁸ ASHP surveyed sterile compounding practices in 1991³⁰ and 1995.³¹ In 1993, ASHP published two guidance documents on this topic: the ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products¹³⁹ and the ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products.¹⁴⁰ ASHP published two books related to sterile compounding: *Infusion Technology Manual* in 1993¹⁴¹ and *Principles of Sterile Product Preparation* in 1995.¹⁴² In 1992, USP published guidance about dispensing sterile drug products intended for home use.¹⁴³ In 1995, a model sterile compounding facility was independently designed and evaluated.¹⁴⁴ In the 1990s, continuing education about sterile compounding was provided at ASHP's professional educational meetings. Parallel to this, compounding in non-health-system settings had increased, and IACP was

founded in 1991.¹⁴⁵ An FDA alert in 1994 about the hazards of precipitates in i.v. therapy brought renewed attention to the need for careful procedures in sterile compounding.¹⁰⁴ In 1998, ASHP and A.S.P.E.N. jointly developed and published guidance about safe practices for parenteral nutrition formulation.¹⁴⁶ In 2000, ASHP published Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures⁷³ and, in the same year, Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products.¹⁴⁷ In 2001, drug shortages had become common, and ASHP established an informational website about shortages to assist health-system pharmacists.¹⁴⁸

All these actions were helpful, but the guidelines were not legally enforceable. In 2004, that changed. USP updated related content in the *United States Pharmacopeia* and moved key content to a legally enforceable chapter (chapter 797).^{57,58,149} This had a huge effect on sterile compounding. In chapter 797, risk categories were established for various types of sterile compounding, and appropriate requirements were established for each level in terms of facilities, starting ingredients, beyond-use dating, staff garb, environmental surveillance, and other factors. The lowest risk level is for compounded preparations made aseptically by the assembly of components that are already sterile. The highest risk level is for preparations made from components that initially are not sterile. Such compounding is necessary in some cases because a suitable manufactured injection is not available to use as a starting ingredient. In such cases, some sort of sterilization process must be used—for example, dry or steam heat if the molecules will withstand it or membrane filtration. Especially for higher risk preparations, some hospitals and home infusion operations lacked the facilities and other resources necessary to

meet many of the requirements and immediately had to reassess whether they could continue compounding some specific preparations.¹⁵⁰ As noted earlier, shortages of manufactured injections added to the dilemma for hospitals. Compounding pharmacies advertised that they could make the needed preparations; therefore, many hospitals turned to them as sources of supply. A survey in 2011 indicated that 66% of hospitals purchased some sterile preparations from compounding pharmacies.¹⁵¹

In 2006, ASHP published a training video and workbook about the basics of aseptic compounding^{152,153} and a video and workbook about the safe handling of drugs hazardous to workers.^{154,155} Also in 2006, an accreditation process was established by the Pharmacy Compounding Accreditation Board to independently assess the capacity of pharmacies to safely and accurately compound medications.¹⁵⁶ That avenue has some potential for assuring quality in compounding, but only 171 of the estimated 7500 compounding pharmacies have become accredited. Only one level of accreditation is available; a separate level for sterile compounding does not exist. It is still early in the life of the accreditation body to know whether it will be able to successfully differentiate pharmacies that achieve sterile compounding safely. The standards for accreditation must be kept consistent with the evolving requirements for sterile compounding. In order to generate and maintain public confidence, it will be necessary for accredited sites to produce consistently preparations with proven efficacy, safety, and quality.

In 1999, the Latiolais Leadership Program at Ohio State University conducted a consensus development conference on the safety of i.v. drug delivery systems.¹⁵⁷ Manufactured parenteral products were rated as the safest, followed closely by preparations compounded in i.v. admixture services. In 2008, a second consensus

conference was conducted¹⁵⁸; again, manufactured parenterals were seen as the most desirable. Sterile compounders were noted as having difficulties in meeting USP's chapter 797 standards. In 2008 and 2009, ASHP published additional videos and workbooks about sterile compounding.¹⁵⁹⁻¹⁶² Also in 2008, USP published a guidebook about compounding sterile preparations.¹⁶³ In 2010, ASHP published guidelines about outsourcing sterile compounding services.¹⁶⁴ In 2011, the Institute for Safe Medication Practices (ISMP) conducted a sterile preparation compounding safety summit that generated guidelines for the safe preparation of sterile compounds.¹⁶⁵ In 2011, ASHP published an electronic interactive handbook on injectable drugs,¹⁶⁶ and the ASHP Research and Education Foundation released an assessment tool for evaluating external compounding pharmacies as potential sources of production and supply for compounded preparations.¹⁶⁷ Also in 2011, ASHP published a book about smart infusion pumps.¹⁶⁸ In 2012, ASHP published additional videos and a workbook about sterile compounding.¹⁶⁹⁻¹⁷² At this writing in early 2013, a new ASHP guidelines document about compounding sterile preparations is under development and is intended to replace the 2000 ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products.¹⁴⁷

All of the above is a record of strong professional leadership aimed at making sterile compounding and i.v. therapy safe. Guidelines, standards, and education have been made abundantly available to pharmacists in all settings. Yet problems have continued.

Legislative and regulatory responses

Laws and regulations about the making of sterile drugs played a significant role (to some extent by their absence) in the evolution of sterile

compounding in hospitals. Strict and enforced federal laws and regulations apply to the manufacturing of sterile drug products. To date, compounding has been viewed as a pharmacy practice, which is regulated at the state level. When sterile compounding expanded, that did not change. When large-scale compounding pharmacies evolved, they sought and obtained licenses as pharmacies. During the years when sterile compounding surged, many of the state regulatory agencies were populated by pharmacists who lacked ongoing familiarity with sterile compounding. The state agencies did not develop extensive regulations and enforcement capacity related to sterile compounding.

As a mission priority, FDA focuses most of its attention on manufacturers, but accumulated adverse events eventually led the agency to become concerned that some compounding pharmacies, despite their being licensed as pharmacies, were engaging in volumes of production and other behaviors that more closely resembled manufacturing than extemporaneous compounding (behaviors such as making large batches of preparations stored for extended periods, lacking identifiable patients for whom preparations were specifically intended, shipping of preparations across state lines, and advertising specific preparations as commodities). These concerns led FDA to release a compliance guide in 1992 that attempted to delineate the mix of factors that would help categorize the type of production occurring (compounding or manufacturing).¹⁷³ The guide provoked worries among compounding pharmacies that they would be required to meet the standards of production for manufacturers.

In 1997, building on FDA's experience in applying the 1992 compliance guide,¹⁷³ the Food and Drug Administration Modernization Act was amended to clarify and expand

FDA's authority to regulate compounding.¹⁷⁴ Among its provisions was a prohibition of advertising specific drug preparations. By 2002, the 1997 modernization act had been challenged in the courts. In 2002, the provisions in the act prohibiting the advertising or promotion of specific compounded preparations were overturned by the U.S. Supreme Court.¹⁷⁵ Importantly, the court did not disagree with a lower court's view that the compounding provisions of the law were unseverable. Therefore, all of the compounding provisions became invalid. In 2003, the Congress defeated an effort to establish an FDA oversight committee on compounding.¹⁷⁶ In 2007, the Congress defeated legislation that would have authorized FDA to establish requirements for sterile compounding and to limit interstate distribution of compounded drugs.¹⁷⁶

In early 2013, FDA conducted inspections of many compounding pharmacies and found numerous deficiencies.¹⁷⁷ At this writing in early 2013, public policymakers seem poised to make changes to laws and regulations about sterile compounding.^{178,179} Their primary focus currently is on large-scale compounding pharmacies because many of the recent injuries and deaths have occurred from preparations made in those settings. This public response is similar to past circumstances that led to statutory and regulatory changes. In 1938, federal laws first required safety assessments of new drug products.¹⁸⁰ That evolved after the deaths of more than 100 people who consumed an elixir containing a vehicle that proved to be toxic. In 1962, federal laws changed to require that new drug products have proven safety and effectiveness.¹⁸¹ That change occurred after birth defects were caused by thalidomide (which was on the market in much of the world but not in the United States).

Sound standards and assessments exist for determining the accept-

ability of manufactured drug products. However, there are additional things about manufacturers of drug products (original and generic) that purchasers cannot readily determine. How many attempts are typically required for a manufacturer to achieve a batch of a product that meets standards? How often has a manufacturer been unable to meet demand? If other manufacturers become unable to produce products on a timely basis, how much extra capacity does a manufacturer have to expand production? Has the manufacturer experienced FDA-mandated plant closures? Has the manufacturer recalled products because of safety concerns? These and probably many other parameters about a manufacturer's performance (and consistency in performance) could be established to grade manufacturers. Would such grading lead purchasers to favor highly graded manufacturers when making source decisions in purchasing? If so, poorer performers might leave the market, and higher performers might be incentivized to prevent shortages. FDA staff members have recently expressed interest in some kind of grading approach, if purchasers would respond positively to it.⁹³

Unique sterile medications that are not available from manufacturers will continue to be a medical necessity for many patients. Also, as good as sterile compounding can be in well-resourced hospitals, some institutions simply are unable to afford the facilities, staff, and procedures necessary to compound even medium-risk preparations. Since manufacturers cannot make all of the unique products needed, the need continues for facilities capable of meeting the stringent facility and procedural requirements for compounding such preparations safely. Since sterile compounding occurs in multiple settings, federal and state lawmakers and regulators must devise appropriate provisions, based on risk levels and

sound ongoing quality assurance, for sterile production in all of those settings. The requirements must be rigidly enforced. Distinct categories should be established for the ongoing surveillance of manufacturers, large-scale compounding pharmacies, hospitals, home infusion pharmacies, and community pharmacies. When it is necessary to use a compounded sterile preparation therapeutically, the pharmacy that compounded the preparation should be stated on the preparation's label.

Some perspectives

Remarkably, we do not know exactly how much sterile compounding occurs or where it happens. Moreover, the actual prevalence of adverse events associated with sterile compounding is unknown. A national public health goal could be established to create such data on an ongoing basis and to target improvements.

We have very good USP standards for sterile compounding. We know the facilities and procedures required, and we have abundant experience in successfully compounding sterile preparations that way. There is a hazard, however, that hospital and home infusion pharmacists could view with some complacency the history of successful adaptation, innovation, and progress with respect to sterile compounding in their settings, especially given the record of harm that has accumulated in recent years with respect to some preparations made in large-scale compounding pharmacies. However, it must be recognized and emphasized that contamination has occurred in multiple compounding settings, and, again, we do not know the collective dimensions of the problems. Would increased surveillance of hospital and home infusion compounding reveal heretofore undetected lapses that need attention? The tragedies of the past should serve as a reminder that unrelenting attention must be applied by pharmacists in all settings

to ensure that sterility is achieved in sterile compounding.

All pharmacists and pharmacy technicians engaged in sterile compounding should be educated, trained for proficiency, certified, and licensed to engage in the activity. Moreover, they should be required to engage in documented periodic refresh training to ensure (through testing and verification of preparations) that they sustain the knowledge, skills, and abilities to carry out sterile compounding safely. A national public health goal (with specific date targets) to achieve the needed education and training would be helpful. Training courses about sterile compounding should be established for pharmacists and pharmacy technicians (there probably is not a need to have separate courses for them). These could be established by pharmacy schools and colleges, professional associations, community colleges and vocational centers, or independent entrepreneurs. To ensure consistent quality, the programs should be accredited by the Accreditation Council for Pharmacy Education.

An important thread in the history of sterile compounding is that hospital pharmacy practice leaders detected problems in the handling of sterile medications very early, and they moved forthrightly to address the problems. There were notable leaders in that history, including Herbert L. Flack, William M. Heller, Kenneth N. Barker, Kenneth E. Avis, and Lawrence A. Trissel. Without their commitment, progress might have been slower or nonexistent. No doubt, thousands of patients owe their lives to these and other pharmacists who helped to improve sterile compounding. Organizations that have been leaders in improving sterile compounding include ASHP, A.S.P.E.N., ISMP, and USP. Their guidelines and requirements, consensus events, publications, and continuing education have provided crucial

information to enable pharmacists to accomplish sterile compounding safely. ISMP deserves special commendation for its cogent analyses and commentaries about safe practices in sterile compounding.^{118,182,183}

As has been noted, when injections are in short supply, sterile compounding increases. The factors that contribute to shortages of manufactured sterile drug products must be reexamined with a commitment to eliminate or mitigate shortages.

While we must continue to strive for zero defects in sterile compounding, a logical question is whether, during compounding, the aseptic assembly of already-sterile manufactured components without a final sterilization step is sufficient, even for the lowest-risk preparations. Given the complexity of sterile compounding, might it be that there is an inherent statistical failure rate with this approach—a rate that realistically we can never totally eliminate? Do we need to think beyond current methods? Might it be possible to devise novel approaches to additionally sterilize final compounded preparations? Is terminal sterilization by radiation (as used in some manufacturing), for example, out of reach for those engaged in sterile compounding? Might there be completely new ways to sterilize final preparations such as through nanoparticles or nanobots that could somehow obliterate microbes and pyrogens in compounded preparations without harming people? Might it be possible to develop ways to immediately detect microbial contaminants in finished preparations without destructive testing? The point is that we should not only continue to apply efforts to accomplish zero defects via the methods we now use. We also should apply innovative thinking to sterile compounding. National goals could be established to develop new methods to enable terminal sterilization of compounded sterile medications and to detect contaminants in

final preparations. Perhaps cash prize incentives could be offered for breakthrough innovations that could be applied widely and cost-effectively.

Conclusion

Over the years, there have been numerous exhortations for voluntary better performance in sterile compounding.^{35-37,184-188} In addition, professional leadership has been vigorous and extensive in the form of guidance, publications, education, enforceable standards, and development of various associations and organizations dealing with safe compounding practices. Yet problems continue to occur. We must engage in diligent learning from the injuries and tragedies that have occurred. Assuming that we are already doing all we can to avoid problems would be an abdication of the professional mission of pharmacists. It would be wrong thinking to assume that the recent problems in large-scale compounding pharmacies are the only problems that warrant attention. It is time for a systematic assessment of the nature and the dimensions of the problems in every type of setting where sterile compounding occurs. It also is time for some innovative thinking about ensuring safety in sterile compounding.

^aTerminology is evolving with respect to sterile drugs. The 2013 edition of the *United States Pharmacopeia* (page 36) uses the terminology “large-volume intravenous solution.”⁹ Therefore, in this article, the abbreviation LVIS is used where it is appropriate, rather than the more common usage of “large volume parenteral” (since the term “large-volume parenteral” applies to both intravenous and irrigation fluids). The 2011 edition of the *United States Pharmacopeia* further explains: “. . . the designation large-volume intravenous solution applies to a single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing more than 100 mL. The designation small-volume injection applies to an injection that is packaged in containers labeled as containing 100 mL or less.”¹⁰ Therefore, in this article, the abbreviation SVI is used, where it is appropriate.

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