

Pharmacy

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ABSTRACT

Patient morbidity and mortality can result from contaminated pharmaceuticals. Pharmacy is responsible for preparation and storage of most sterile medication. It may be necessary for pharmacy personnel to participate in identifying patients who have received specific products associated with epidemics. Pharmacy personnel are responsible for coordinating recalls of pharmaceutical preparations, such as occurs in cases of intrinsic contamination. The pharmacy department should participate in multidisciplinary activities such as quality assurance teams, infection control committees, and antimicrobial use programs to ensure appropriate preparation and use of pharmaceuticals.

KEY CONCEPTS

- Risks associated with contamination of sterile products
- Modes of contamination of sterile pharmaceutical products
- Methods for preventing contamination of sterile products
- Pharmacy responsibilities involving antimicrobial control

I. BACKGROUND

Patient morbidity and mortality can result from contaminated pharmaceuticals. Pharmacy is responsible for preparation and storage of most sterile medication. It may be necessary for pharmacy personnel to participate in identifying patients who have received specific products associated with epidemics. Pharmacy personnel are responsible for coordinating recalls of pharmaceutical preparations, such as occurs in cases of intrinsic contamination. Other responsibilities of pharmacy departments may include managing intravenous (IV) therapy teams, compounding pharmaceuticals for patients receiving home IV therapy, and compounding enteral nutrition products. The pharmacy department provides oversight of the safe use of medications in other areas of the institution (e.g., inspections for outdated medication and monitoring of refrigerated medication storage space). The pharmacy also provides information on pharmaceuticals including indications, dosage, route

of administration, contraindications, adverse effects, drug interactions, and proper storage. Pharmacy personnel are not at high risk for occupational exposure to infectious diseases unless they are involved in direct patient care, such as during cardiac arrest response. The pharmacy should work with infection control departments in managing

employee exposure to contagious patients and selection of germicides. Pharmacists may be involved in advocating and administering immunizations (e.g., influenza and pneumococcal vaccines). The pharmacy department should participate in multidisciplinary activities such as quality assurance teams, infection control committees, and antimicrobial use programs to ensure appropriate preparation and use of pharmaceuticals.

II. BASIC PRINCIPLES

Contamination of infusates is an uncommon cause of infections, but may result in epidemics.¹ Intrinsic contamination (that which occurs during the manufacturing process) and extrinsic contamination (that which occurs subsequent to manufacturing, during the admixture process or while the infusate is in use) of infusates are a less frequent cause of infection than cannula-related contamination but are more likely to result in bacteremia and septic shock.¹ Intrinsic and extrinsic contamination are differentiated based on epidemiologic data.

Most nosocomial epidemics of infusion-related septicemia resulting from intrinsic or extrinsic contamination are caused by aerobic gram-negative bacteria.²

Pathogens implicated include the *Enterobacteriaceae* such as *Klebsiella*, *Enterobacter*, *Serratia spp.* and *Citrobacter freundii*, *Burkholderia cepacia* and *Ralstonia pickettii*.¹⁻³

Intrinsic contamination of infusate has led to epidemics of nosocomial sepsis.^{2,3-5} Intrinsic contamination of parenteral medications with endotoxin caused an epidemic of clinical sepsis in a newborn nursery.⁶ Epidemics of *Candida parapsilosis* and *Candida albicans* fungemia have been related to use of contaminated parenteral nutrition (PN).⁷⁻⁹ Epidemics of septicemia caused by *Staphylococcus saprophyticus* and *Enterobacter cloacae* have resulted from contamination of PN admixtures during compounding or storage.^{10,11}

Clusters of postoperative infections have been associated with extrinsic contamination of propofol, an intravenous hypnotic agent in a 1% lipid emulsion; organisms isolated include *Staphylococcus aureus*, *Candida albicans*, *Moraxella osloensis*, *Enterobacter agglomerans* and *Serratia marcescens*.¹²⁻¹⁴ An outbreak of *Serratia marcescens* and *Enterobacter cloacae* bacteremia in a surgical intensive care unit was traced to extrinsic contamination of the parenteral narcotic fentanyl by a respiratory therapist who was drug seeking.¹⁵

In-use IV fluids have contamination rates of 1.9 to 7.8%.¹⁶⁻¹⁹ The most common organism found is coagulase-

negative staphylococci. In addition, free endotoxin was found in 2.5%.¹⁸ In-use syringes of propofol have shown contamination rates of 19/376 (5.1%) and 18/302 (5.6%).^{20,21}

Specific microorganisms have the ability to proliferate in different fluids. *Klebsiella*, *Serratia*, and *Enterobacter* species and *Burkholderia cepacia* can multiply in 5% dextrose.¹ *Candida albicans* can grow slowly,¹ while *Staphylococcus*, *Proteus*, *Escherichia coli*, *Herellea* and *Pseudomonas aeruginosa* die slowly in dextrose.

²² *Burkholderia cepacia*, *Pseudomonas aeruginosa*, *Acinetobacter* and *Serratia* will grow in distilled water.¹ *Pseudomonas aeruginosa*, *Enterobacter* and *Serratia* can grow in lactated Ringer's solutions.

¹ Microbial growth, with the exception of *Candida* species, is possible in 0.9% sodium chloride.²³ Fungi such as *C. albicans* and *Torulopsis glabrata* can grow in PN fluids, albeit very slowly; proliferation did not occur when solutions were stored at 4 °C for 7 days.²⁴ The growth of most bacteria is inhibited in PN solutions. The addition of albumin to PN solutions increases the potential for bacterial and fungal growth.^{7,25} *Staphylococcus aureus*, *E. coli*, *E. cloacae*, *P. aeruginosa*, and *C. albicans* grow in 10% fat emulsion solution.^{23,26,27} *Staphylococcus epidermidis*, *C. albicans*, and *E. coli* survive in total nutrient admixtures (TNA), in which fat emulsion is combined with dextrose and amino acid mixtures.²⁸ *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *Enterococcus faecalis*, and Group JK *Corynebacterium* displayed greater growth in TNAs as compared to PN fluids.²⁹ Propofol supported the growth of *S. aureus*, *E. faecalis*, *P. aeruginosa*, and *C. albicans*; for *P. aeruginosa* and *E. faecalis*, a bactericidal period was followed, after 48 hours, by increasing growth.³⁰ Preparations of midazolam HCl, morphine sulfate, fentanyl citrate, bupivacaine HCl, atracurium besylate, vecuronium bromide, epinephrine, dopamine, dobutamine, norepinephrine, and sodium nitroprusside in normal saline and 5% dextrose in water were bactericidal for *S. aureus*, *E. faecalis*, *P. aeruginosa*, and *E. coli* and did not support growth of *C. albicans* at room temperature over 48–72 hours.³⁰

Contamination of other pharmaceutical products has led to infections. An outbreak of *B. cepacia* caused by contamination of multidose albuterol vials was linked to poor infection control practices, including respiratory therapists carrying vials in their pockets for several days. The pH of some solutions tested was not within the recommended range, and the concentration of preservative fell from baseline after 5 days.³¹ Intrinsically contaminated saline solution used for respiratory therapy has caused clusters of *R. pickettii* respiratory tract colonization.^{32,33} Use of contaminated multidose ophthalmic containers have resulted in *S. marcescens* keratitis³⁴ and *P. aeruginosa* corneal scleritis;³⁵ the organisms were cultured from the container but not

from the solution itself.^{34,35} Bacteria were cultured

from 82/638 in-use multidose ophthalmic solutions;³⁶ on the other hand, 81 opened multidose ophthalmic medications were tested, and no contamination was found.³⁷ Irrigation with a cardioplegic solution contaminated with *E. cloacae* led to an outbreak of sepsis.³⁸ Intrinsic contamination of a non-FDA-approved product labeled “adrenal cortex extract” caused a series of cases of *Mycobacterium abscessus* abscesses in patients who received intramuscular injections.³⁹ Contamination of enteral nutrition has been associated with infections, including septicemia.^{40,41} Many microorganisms, including gram-negative bacteria, gram-positive bacteria and fungi, can proliferate in enteral nutrition preparations.^{40,42,43} Mineral oil used for bathing infants was contaminated with *Listeria monocytogenes*, leading to an outbreak of neonatal listeriosis.

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III. MODES OF CONTAMINATION OF STERILE PHARMACEUTICAL PRODUCTS

Preparation of IV products in areas outside the pharmacy, in areas not providing a class 100 environment (no greater than 100 particles per square foot), has led to various bloodstream infections. Batch preparation of propofol syringes outside a laminar-airflow hood was associated with *S. aureus* bloodstream infections.⁴⁵ *E. cloacae* septicemia resulted from preparation of heparin infusions in an area not specifically designed for such use.⁴⁶ An outbreak of *B. cepacia* sepsis resulted from preparation of heparin infusions for several patients using a single 500-mL bag of dextrose, which was stored near a sink.⁴⁷

Most IV-related infections result from microbial contamination of the cannula and the cannula wound.^{1,2}

Improper aseptic technique has been associated with epidemics. Failure to employ aseptic technique during preparation and administration of propofol combined with inherent properties of this product contributed to extrinsic contamination and resulted in postsurgical infections.^{12,13}

Several epidemics have been traced to use of contaminated multidose vials (MDVs), including an outbreak of fulminant hepatitis B in a hospital that was apparently due to contaminated heparin flush solution.⁴⁸ Subcutaneous *Mycobacterium chelonae* abscesses resulted from contamination of diphtheria-pertussis-tetanuspolio (DPTP) vaccine.⁴⁹ Contamination of diphtheriapertussis-tetanus-polio vaccine was implicated in two outbreaks of group A streptococcal abscesses.⁵⁰ Septic arthritis resulted from intra-articular injections of MDV methylprednisolone contaminated with *B. cepacia*.⁵¹ Contaminated MDVs were the most likely source of outbreaks of hepatitis C virus infections.⁵²

Contamination of in-use vials is rare, according to

recent studies.^{53,54} MDVs were tested for bacterial contamination during a two-phase study: during phase I there was a policy in place to discard MDVs after 14 days, and during phase II, they were discarded after 3 months. No contamination was found during either phase.⁵⁵

An examination of 864 vials in use for up to 402 days found no contamination. The mean duration of use was 18 days, and only 13% were in use for more than 30 days.⁵³ One hundred ninety-seven MDVs were collected that had been entered 1 to 10 times. No bacterial or fungal growth was found.⁵⁶ Cultures from 8 of 68 insulin vials in use for a mean of 111 days grew *Corynebacterium* species or *S. epidermidis*; when recultured, five-eighths did not show growth. None of the positive cultures were associated with infections. No endotoxin was found in any of the samples.⁵⁷ Sixty-nine in-use MDVs were collected; no bacterial contamination was identified, but one vial was contaminated with red blood cells.⁵⁴

For the most part, the contents of MDVs, including preservatives, diluent, and the drug itself do not support microbial growth.⁵⁸⁻⁶⁰ Thirteen strains of microbes were used to deliberately contaminate MDVs of insulin, lidocaine, methohexital sodium, potassium chloride, procainamide, sodium thiopental, sodium heparin, and succinylcholine. Procainamide and methohexital were sterile within 24 hours; in lidocaine there was survival and even proliferation of some gram-negative aerobic bacteria. All others killed the organisms slowly or allowed only limited survival. Survival of microbes was not correlated with the presence of preservatives.⁶⁰ Atropine, lidocaine, and cyanocobalamin were contaminated with *S. aureus*, *P. aeruginosa*, *E. coli*, and *S. marcescens*. The atropine and lidocaine solutions were sterile within 24 hours at room temperature. *S. aureus* in cyanocobalamin was killed slowly.⁵⁸ Undiluted vials of midazolam HCl, morphine sulfate, fentanyl citrate, bupivacaine HCl, atracurium besylate, vecuronium bromide, epinephrine, dopamine, dobutamine, norepinephrine, and sodium nitroprusside were bactericidal for *S. aureus*, *E. faecalis*, *P. aeruginosa*, and *E. coli* and did not support growth of *C. albicans* at room temperature over 48–72 hours.²⁹ Single-dose vials of gadolinium-based contrast media were inoculated with *S. aureus*, *S. epidermidis*, *Corynebacterium jeikeium*, *Bacillus*, *Serratia odorifera*, *Xanthomonas maltophilia*, or *C. albicans* and stored at room temperature or at 4°C. All organisms except *S. odorifera* persisted at 48 hours; *S. aureus*, *S. epidermidis*, and *C. jeikeium* were still present at 7 days.⁶¹ Most experimentally contaminated MDVs of anesthetic agents became sterile within 24 hours.⁵⁹ Human immunodeficiency virus (HIV) was detectable

up to four hours following deliberate contamination of MDVs of lidocaine containing epinephrine.⁶² MDVs were deliberately contaminated by several different

methods. These methods were: entering the vial without first swabbing, touching the rubber septum to the skin, swabbing the rubber septum with an alcohol wipe that had been dipped into a solution of 10⁷ CFU of bacteria, leaving the contaminated wipe on the septum for 20 minutes, contaminating the needle with the bacterial solution before withdrawing the medication, and adding 0.1 mL of the bacterial solution to the vial. With the first three methods, little or no growth occurred. For the last three methods, almost all vials showed heavy growth.⁵⁶ Insulin vials deliberately contaminated with *S. aureus* and *P. aeruginosa* were sterile by 24 hours at room temperature; *P. aeruginosa* was killed more slowly at 4°C.⁵⁷ Contaminated vials could be pathogenic even if sterile; following deliberate contamination with *B. (Pseudomonas) cepacia*, a vial of lidocaine had endotoxin, as did a vial of insulin contaminated with *Enterococci*.⁶⁰ Equipment used in preparing intravenous admixtures can be a source of contamination.^{7,8}

Methods for Preventing Contamination of Sterile Products

The Centers for Disease Control and Prevention (CDC) recommends all parenteral fluids be prepared in the pharmacy using a laminar-airflow hood.⁶³ The Intravenous Nursing Society Standards of Practice recommends that an IV admixing program be established and conducted under the direction of the pharmacy. When nurses prepare IV admixtures, they should do so with the use of a laminar-airflow hood.⁶⁴

All sterile products should be prepared in a Class 100 environment,⁶⁵ which can be obtained with the use of a certified vertical- or horizontal-laminar-airflow hood. Laminar-airflow hoods should be operated continuously. Before processing products in the hood, it should be in operation for a period of time long enough to purge room air from the work area. All work should be done at least 6 inches inside the hood. The work surface and all accessible interior surfaces of the hood should be disinfected with an appropriate agent before work begins and periodically thereafter. Exterior surfaces of the hood should be cleaned periodically. The American Society of Health-System Pharmacists (ASHP) recommends that laminar-airflow hoods be certified biannually or when they are relocated.⁶⁵ Certification should be performed by a qualified contractor.⁶⁶

In order to minimize the risk of contamination, sterile products should be prepared in an area functionally separate from other areas. The *ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile*

*Products*⁶⁵ recommends that the hood be situated in a “controlled area” that meets either class 100,000 (no greater than 100,000 particles per square foot) or 10,000 conditions (depending of the risk level of the products being compounded) for acceptable airborne

particle levels. Class 10,000 conditions (no greater than 10,000 particles per square foot) can usually be met without use of a clean room.^{67,68} The sterile product preparation area should be one in which airflow and personnel traffic are limited. The ASHP recommends using a “limited access” area, separate from other pharmacy areas. This could be achieved by using a separate room or partitioned area. The materials surrounding the sterile preparation area should be nonparticle shedding. Particle-generating items such as cardboard boxes should not be stored in the area surrounding the hood. Air ducts and vents should not interfere with the airflow in the preparation area. The use of special walls, flooring, and ceilings (clean rooms) is not necessary. However, use of materials such as carpeting, drapes, and other particulate generating material is not acceptable. Personnel preparing sterile products should consider wearing special clothing covers that generate low amounts of particles. The ASHP⁶⁵ recommends use of protective clothing covers including gowns, masks, and coverings for head and facial hair. However, at least one study has shown that special dress does not affect contamination rates.⁶⁹ The sterile product preparation area should have handwashing facilities with hot and cold running water. Personnel should clean hands and forearms with an antimicrobial-containing soap or detergent before preparing sterile products. Eating, drinking, and smoking should not be allowed in the preparation area. The containers of the ingredients used for compounding the sterile product should be inspected for defects, expiration date, and product integrity before use. If the product is defective or has expired, it should not be used. Defective products should be promptly reported to the FDA.⁷⁰

The rubber stoppers of containers should be wiped or sprayed with 70% alcohol before entry. The ASHP recommends that the entire surface of ampuls, vials, and container closures be disinfected appropriately before placement in the laminar-airflow hood.⁶⁵ Automated devices used for compounding sterile products that are placed in the laminar-airflow hood should first be disinfected. Personnel should avoid touch contamination of sterile supplies.

In 2002, five cases of *Exophiala dermatitidis* infection associated with injectable methylprednisolone acetate were reported to the CDC. The methylprednisolone had been prepared at a compounding pharmacy later found to have improper performance of an autoclave with no written procedures for autoclave prepara-

tion, no testing for sterility or appropriate checking of quality indicators, and inadequate clean room practices as outlined in the ASHP guidelines for pharmacy-prepared products. Four patients developed meningitis after epidural injections, resulting in one death, and one patient developed sacroiliitis after intra-articular injections. Cases occurred as late as 152 days following

an injection.⁷¹

Several factors must be considered in assessing the sterility of MDVs.^{72,73} The aseptic technique of individuals likely to enter specific vials is an important factor in determining sterility; improper aseptic technique has been identified in healthcare workers.^{74,75} The environment in which the vial will be entered is also important, such as sterility of the environment where vials are entered (i.e., laminar-airflow hoods versus patient care units) and situations under which vials are opened (e.g., MDVs on cardiac arrest carts are often entered without careful attention to aseptic technique and should be discarded after the first use).^{73,76} The U.S. Pharmacopoeia (USP) procedure for testing effectiveness of preservatives in MDVs does not require killing of all microorganisms but rather inhibition of proliferation of the microorganisms.⁷⁶ The concentration of preservatives cannot be increased to unsafe levels.⁵⁰ Many drug preparations appear to have sterilizing properties irrespective of the presence of preservatives.⁵ The effects of refrigeration on the bactericidal activity of preservative in MDV should be considered in setting policy.⁵⁸ Solutions containing preservatives (phenol, methylparaben, and benzyl) and inoculated with *S. aureus*, *P. aeruginosa*, *E. coli*, and *S. marcescens* show persistence of bacteria longer under refrigeration than at room temperature.^{58,64} The number of entries may affect sterility of MDVs; however, there is no practical way to document this. In addition, frequent use may cause vials to be used up more rapidly, thereby actually reducing the risk of infection.⁵³ Setting time limits after first opening can help ensure sterility and stability:

1. Manufacturers' expiration dates apply to stability and sterility of unopened vials.
2. There are no specific guidelines with respect to expiration of opened MDVs.^{63,73} The USP considers "any time limit put on the use of a multipledose vial after its first opening as strictly arbitrary."⁷³
3. Discarding MDVs after one use is probably not necessary.
4. Some sources recommend dating all opened vials, although there is no evidence that dating vials has any effect on sterility.^{53,54}

5. Expiration of vials may need to vary according to other factors that affect sterility.

The CDC recommends use of single-dose vials whenever possible for admixture of parenteral products.⁶³ However, this may not be practical for IV admixture programs for reasons of economy and efficiency. When MDVs are used, the CDC recommends refrigerating the vials after opening if recommended by the manufacturer, cleaning the rubber diaphragm of the vial with alcohol before inserting a device into the vial, using a sterile device each time a vial is accessed, and avoiding touch contamination of the device before penetrating the rubber diaphragm. The MDV should be discarded when empty, when suspected or visible

contamination occurs, or when the manufacturer's stated expiration date is reached.⁶³

The final sterile product should be examined for any leaks, cracks, turbidity, or particulate matter. Bacterial growth may not be obvious, even in concentrations of 10⁶/mL.^{22,63} The ASHP⁶⁵ recommends a label be attached to all admixed parenterals and include the following information:

1. For patient-specific products: the patient's name and any other appropriate patient identification (e.g., location, identification number); for batch-prepared products: control or lot number
2. All solution and ingredient names, amounts, strengths, and concentrations (when applicable)
3. Expiration date and time, when applicable
4. Prescribed administration regimen, when appropriate (including rate and route of administration)
5. Appropriate auxiliary labeling (including precautions)
6. Storage requirements
7. Identification of the responsible pharmacist (and technician)
8. Device-specific instructions (when appropriate)
9. Any additional information, in accordance with state or federal requirements

Storage of pharmaceuticals that are to be used to admix parenterals should be according to manufacturers' recommendations. Admixed parenterals may be stored in the refrigerator for up to 1 week, providing that refrigeration begins immediately after preparation and is continuous. Stability of ingredients may dictate a shorter storage time. The ASHP indicates that, depending on the sterile product preparation procedures used and the storage temperature, the admixed parenteral products may be stored for longer periods of time.⁶

The CDC has not made recommendations for the hang time of IV fluids (including nonlipid-containing parenteral nutrition fluids). Lipid-containing PN fluids should be completed within 24 hours of hanging the fluid.⁶³ The CDC recommends that infusion times for lipid emulsions not part of a total nutrient admixture should be no more than 12 hours.⁶³ However, some manufacturers of lipid emulsions support a 24-hour hang time.⁷⁷

The manufacturers of propofol recommend that the drug be stored at room temperature; refrigeration is not recommended. If the drug is used directly from the prefilled syringe or vial, it should be used within 12 hours. Tubing and any unused portions of propofol vials should be discarded after 12 hours. However, if propofol is transferred to a syringe or other container prior to administration, the drug should be discarded and administration lines changed after 6 hours. Strict aseptic technique must be maintained in handling even though a preservative (EDTA or sodium metabisulfite) has been added.⁷⁸

The pharmacy should monitor for appropriate storage

of pharmaceuticals throughout the institution. Routine inspections should be performed to ensure that expired medications are removed from patient care areas and disposed of properly. Temperatures of refrigerators and freezers used to store pharmaceuticals should be closely monitored and recorded daily.

For preparations given a high risk level, the ASHP⁶⁵ recommends establishing criteria for monitoring the environment, including air quality and work surfaces. The ASHP⁶⁵ recommends sterilization and quarantine for high-risk products; efficacy of the sterilization process should be validated. The ASHP recommends that quality assurance procedures be developed to validate aseptic technique for each person preparing sterile products. Revalidation should occur annually or “whenever the quality assurance program yields an unacceptable result, and whenever unacceptable techniques are observed.”⁶⁵

Pharmacy Responsibilities involving Antimicrobial Control

Concerns about resistance causing increased morbidity, mortality, and costs of healthcare have led to recommendations to control antimicrobial use.^{79,80} Multidisciplinary groups, including pharmacists, should establish a system for monitoring resistance and antibiotic usage, establish practice guidelines and other policies to control the use of antibiotics and respond to data from the monitoring system, and measure outcomes to evaluate the effectiveness of policies. Microbiologists should work with infectious disease clinicians, pharmacists, hospital epidemiologists, infection control profes-

sionals, and representatives of clinical departments to choose the drugs that will be tested and routinely reported. Specific responsibilities for pharmacy personnel include generation and analysis of data to determine compliance with restriction policies, participation in development of programs for formulary and antimicrobial controls, responsibility for computer medication order entry systems, and in collaboration with physicians, patient-specific recommendations for optimal antimicrobial use.

IV. SUMMARY AND CONCLUSIONS

Pharmacy is responsible for preparation and storage of most sterile medication. The pharmacy department should participate in multidisciplinary activities such as quality assurance teams, infection control committees, and antimicrobial use programs to ensure appropriate preparation and use of pharmaceuticals and sterile products.

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SUPPLEMENTAL RESOURCES

American Society of Health-System Pharmacists (ASHP):
www.ashp.org

Centers for Disease Control and Prevention (CDC): www.cdc.gov

Food and Drug Administration (FDA): www.fda.gov

Intravenous Nursing Society (INS): www.ins1.org

United States Pharmacopeial Convention, Inc. (USP): www.usp.org