I.V. admixture contamination rates: Traditional practice site versus a class 1000 cleanroom

MARK THOMAS, MICHAEL D. SANBORN, AND RICK COULDRY

Purpose. The contamination rates associated with the preparation of medium-risk i.v. admixtures in a traditional practice site and in a class 1000 cleanroom were compared.

Methods. Simulated product media fills served as the samples. Each investigator, a pharmacist and a pharmacy technician, prepared 500 vials and 500 small-volume parenteral (SVP) bags in five separate runs at a traditional practice site and in a cleanroom. *United States Pharmacopeia* chapter 797 medium-risk compounding procedures were followed, and strict adherence to aseptic technique was employed. Single-strength tryptic soy broth was substituted for the drug and diluent in the admixtures. Positive and negative controls were also prepared and stored for the duration of the study. The pharmacist and technician prepared a total of 4057 samples: 2027 samples (1014 vials and 1013 SVP bags) were prepared in a class 1000 cleanroom, and 2030 (1014 vials and 1016 SVP bags) were prepared at a traditional practice site.

Results. Contamination rates did not significantly differ between the traditional practice site (0.296%) and the cleanroom environment (0.344%) ($p = 1.0$). A significant difference in the number of contaminated samples was found between the two investigators (2 of 2057 were contaminated by the pharmacist and 11 of 2000 were contaminated by the technician) ($p = 0.012$). Contamination rates by the pharmacist ($p = 1.0$) and technician ($p = 1.0$) did not significantly differ between sites.

Conclusion. The most important variable affecting microbial contamination of admixtures was the aseptic technique of personnel, not the environment in which the drugs were compounded.

Index terms: Additives; Aseptic areas; Compounding; Contamination; Control, quality; Injections; Personnel, pharmacy; Pharmacists

Am J Health-Syst Pharm. 2005; 62:2386-92

Surveys of hospital pharmacists suggest that, while guidelines regarding i.v. preparations have existed for many years, most pharmacies have been slow to adopt recommendations regarding the compounding environment, training of personnel, and quality assurance. National surveys conducted by the American Society of Health-System Pharmacists (ASHP) in 1995 and 2002 failed to show significant changes in the sterile compounding practices of hospital pharmacists.[1,2]

Requirements that mandate procedures and environmental safeguards, including the use of a cleanroom environment for the preparation of sterile admixtures in hospitals, have been published in chapter 797 in the *United States Pharmacopeia* (*USP*).[3] *USP* chapter 797 is also being incorporated into the Joint Commission on Accreditation of Healthcare Organization's survey process and will likely be adopted by many state boards of pharmacy. Most pharmacies are planning for or completing the renovations necessary for such an environment, and the costs associated with these changes are significant.

The importance of environmental hygiene for the processing of sterile admixtures has been stressed for a number of years. A study evaluating the effect of laminar airflow (LAF) and cleanroom garb revealed that the rate of contamination of admixtures compounded in LAF hoods (2 of 650 total samples were contaminated) was significantly less than that for those compounded on a clean tabletop (9 of 650 samples were contaminated) ($p = 0.05$), regardless of the operator's dress.[4] The study also found that cleanroom garb had no apparent effect on the outcome of contamination rates of admixtures, regardless of the environment in which the admixture was prepared.

MARK THOMAS, M.S., B.S., is Director of Pharmacy, Cook Children's Medical Center, Fort Worth, TX. MICHAEL D. SANBORN, M.S., B.S., FASHP, is System Director of Pharmacy Services, Baylor University Medical Center, Dallas, TX. RICK COULDRY, M.S., B.S., is Director of Pharmacy, Department of Pharmacy, University of Kansas Hospital, Kansas City.

Address correspondence to Mr. Sanborn at Baylor University Medical Center, 3500 Gaston Avenue, Dallas, TX 75246 (mikesa@baylorhealth.edu).

DOI 10.2146/ajhp050078

Another study compared the contamination rates of admixtures prepared in the LAF hood and admixtures prepared on the nursing unit by nurses.[5] The rate of contamination was higher in admixtures prepared on the nursing unit versus those prepared in the LAF hood (10.9% versus 5.5%, respectively). Touch contamination played a major role in the contaminated samples, demonstrating the importance of strict aseptic technique.

I.V. admixture contamination rates reported in the literature range from 0% to 14.5% (Table 1).[4-19] Studies that tested for contamination using simulated product media fills had the lowest reported contamination rates, suggesting a lower frequency of adventitious contamination with this method.[7-11,18,19] Further, Trissel et al.'s[18,19] two independent benchmark contamination rate studies demonstrated a much higher contamination rate in the cleanroom versus the noncleanroom setting (5.2% versus <0.1%, respectively).

To date, no published studies have directly compared the contamination rates of cleanrooms with traditional compounding environments. The purpose of this study was to compare the contamination rates of medium-risk compounding of simulated product media fills prepared under traditional practice conditions and under class 1000 cleanroom conditions.

Methods

The compounding process used in this study was designed to simulate chapter 797 medium-risk compounding using batch preparation of an i.v. admixture that required reconstitution of the drug and subsequent transfer to an i.v. piggyback.

Sample preparation. Simulated product media fills served as the samples. Each investigator prepared admixtures using aseptic transfer. Single-strength tryptic soy broth[a] (TSB) was substituted for each component of the admixture (drug and diluent).

The diluent consisted of 1000 mL of single-strength TSB in a 1-L polyvinyl chloride (PVC) bag simulating a 1-L bag of sterile water for injection. Empty sterilized 30-mL vials were used to simulate the drug component. Thirty milliliters of TSB was transferred into these empty vials from the diluent bag, the vials were shaken to simulate reconstitution, and the contents were transferred from the vial into the final container, an empty 50-mL small-volume-parenteral (SVP) bag. The TSB was transferred, using aseptic technique, simulating the actual admixture production process. Turbidity was measured by direct examination of the simulated product after incubation.

Samples were prepared following identical preparation procedures at two different sites. At the first site, media fills were prepared under traditional practice conditions, similar to those described in the ASHP National Survey of Quality Assurance Activities for Pharmacy-Prepared

Table 1.
Summary of Studies Evaluating I.V. Contamination Rates Using Various Sampling Methods and Environments

Ref.	*n*	Sampling Method(s)	Laminar-Airflow Workbench?	Contamination Rate (%)
4	700	Direct transfer, USP	Yes	0.29
	700	Direct transfer, USP	No	1.29
5	55	Membrane filtration, USP; direct transfer, USP	Yes	5.5
	54	Membrane filtration, USP; direct transfer, USP	Yes	5.6
	55	Membrane filtration, USP; direct transfer, USP	No	7.3
	55	Membrane filtration, USP; direct transfer, USP	No	10.9
6	210	Membrane filtration, USP	Yes	1.9
	215	Membrane filtration, USP	Yes	3.7
7	168	Media fills, simulated product	Yes	0.0
8	450	Media fills, simulated product	Yes	0.0
9	405	Media fills, simulated product	Yes	0.0
10	50	Media fills, simulated product	Yes	0.0
	50	Addi-Chek filtration[a]	Yes	0.0
11	360	Media fills, simulated product (modified)	Yes	0.0
12	104	Membrane filtration	Yes	0.0
13	236	Direct transfer, USP	Yes	3.8
14	906	Direct transfer, USP	Yes	3.97
15	79	Membrane filtration[b]	Yes	5.1
	76	Membrane filtration[b]	Yes	5.3
16	186	Membrane filtration	No	5.38
17	350	Direct transfer, USP	Yes	12.2
	350	Direct transfer, USP	No	14.5
18	1035	Media fills, simulated product	Yes	0.0
19	539	Media fills, simulated product	Yes	5.2

[a]Millipore Corp., Bedford, MA.
[b]0.5-μm inline filter.

Sterile Products in Hospitals.[20] The pharmacy included a limited-access room (91 sq ft) dedicated to sterile admixture production, where pharmacy personnel prepared sterile admixtures without gloves, low-shed garments, masks, hair covers, or shoe covers. The limited-access room had one doorless entrance, no anteroom or product preparation room, stock shelves with i.v. fluids and drugs, and an unfiltered air supply. The room held two freestanding, inspected, and certified class 100 LAF hoods, a vertical LAF hood for compounding antineoplastics, and a horizontal LAF hood for compounding SVPs and large-volume parenterals. All samples at this site were prepared in the same class 100 horizontal LAF hood (EdgeGARD, Baker Co., Sanford, MA). Figure 1 depicts the floor diagram of the pharmacy area.

The second compounding site employed an International Standards Organization (ISO) class 6 (class 1000) cleanroom (288 sq ft) with an entrance from an ISO class 7 gowning room and an exit to an ISO class 7 product preparation room. Access to the gowning room required passing through an ISO class 8 anteroom. The cleanroom had positive pressure (≥0.05 in of water) and was supplied with high-efficiency particulate air (HEPA) filtered air (39.6 air exchanges/hr), with particle-free walls, floors, and ceilings. The compounding equipment consisted of two freestanding, inspected, and certified vertical LAF hoods and one metal frame workbench. Before entering the cleanroom, pharmacy personnel donned a low-shed gown over surgical scrubs, sterile gloves (double gloved), a hair cover, a mask, and shoe coverings. All samples in this site were prepared in the same class 100 vertical LAF hood (Nuaire, Plymouth, MN). Figure 2 outlines the floor diagram of the cleanroom and surrounding areas.

Aseptic technique, an important component of this study, was strictly followed at both sites. Two investigators (a pharmacy student who had five years of experience in preparing i.v. admixtures as a pharmacy technician and a pharmacist with two years of experience as a pharmacist in charge of an i.v. room and who had trained numerous personnel in aseptic technique) prepared the samples at each site. Both investigators had previously been evaluated for and proven competent in aseptic technique in both horizontal and vertical LAF hood environments via didactic training and visual observation. Each investigator prepared at least 500 vials and 500 SVP bags in 5 separate runs at the traditional practice and cleanroom sites. At least 100 vials and 100 bags were prepared per run, meaning that at least 2000 samples were prepared within 10 runs per site.

Aseptic transfer. The aseptic transfer procedures used at both sites were identical, allowing for differences in LAF hood configurations (horizontal versus vertical). Differences occurred only during pretransfer and posttransfer procedures, due to special requirements dictated by the policies and procedures of the cleanroom site, which included donning cleanroom garments, spraying equipment with 70% isopropyl alcohol before taking it into the cleanroom, and labeling the SVP bags outside the cleanroom in the product preparation room. When using the LAF hoods, aseptic transfer procedures were identical. The investigators assembled all necessary equipment before entering the hoods.

Investigators at the traditional site washed their hands for two to three minutes using a 4% chlorhexidine antimicrobial soap and dried their hands with a paper towel. Investigators at the cleanroom site used a surgical scrub brush with parachlorometaxylenol for the same period of time and dried their hands with a motorized air hand drier. The investigators rewashed their hands upon returning anytime they left the compounding area.

Each bag was numbered in the order in which it was prepared. At the traditional practice site, the bags were removed from the LAF hood and labeled while still in the i.v. room. In the cleanroom, labels were affixed to the bags in the product preparation room adjacent to but separate from the cleanroom.

Figure 1. Traditional practice-site floor diagram. LAF = laminar airflow.

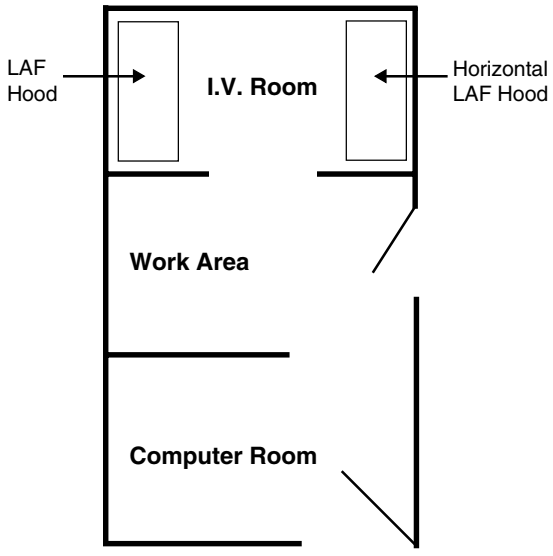
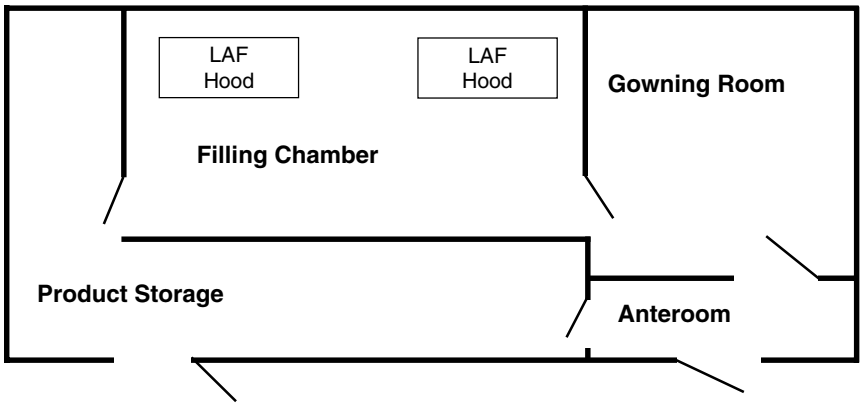


Figure 2. Cleanroom floor diagram. LAF = laminar airflow.



The samples from each site were stored in the same environment and incubated for 14 days at 35 °C. Samples were visually inspected for turbidity on day 7 by the principal investigator and on day 14 by a microbiologist. The microbiologist was not given any information about where the samples were prepared or who prepared them. She had access only to the lot and vial or bag numbers and reported the results using those numbers. When contamination was evident, the organisms were identified by genus by the microbiologist, and the integrity of the container was examined.

Preparation of controls. Positive controls were used throughout the study to determine if the admixtures were capable of supporting growth at minimal exposure. Twenty-four vials and SVP bags were inoculated in a class 100 LAF hood with low concentrations (growth rates in the logarithmic phase, 10^1–10^2 bacteria/mL) of either *Staphylococcus epidermidis* or *Escherichia coli*. The organisms in these controls were identified, after incubation, by the microbiologist to verify that turbidity was attributable to the inoculum. Negative controls (50 SVP bags and five vials) were used to validate the use of aseptic technique. The negative-control SVP bags were prepared by aseptically transferring 20 mL of TSB from one of the diluent bags inside an LAF hood and then incubated for 14 days at 35 °C. Any turbid bags were discarded. Nonturbid vials from the first run were used as negative controls. Five negative-control bags were simultaneously incubated with each of the manipulated product simulation runs. The five negative control vials were kept inside the incubator during the study.

Background microbial load. Viable particle-air samples were taken to determine the background microbial load of the LAF hoods and the immediate surrounding environment. At least three air samples were collected inside the LAF hoods and the rooms containing the LAF hoods using the Biotest RCS Centrifugal Air Sampler (Biotest Diagnostics Corp., Fairfield, NJ). This air sampler quantifies the number of microbial colony-forming units (CFUs) per volume of air. The number of CFUs were counted, averaged, and reported using the following equation:

$$\text{CFUs/m}^3 = (\text{colonies on agar strip} \times 25)/\text{sampling time (min)}$$

Statistical analyses were conducted using a two-tailed Fisher's exact test. This test was selected because of the low frequency of contamination expected at both sites.

Results

The number of samples prepared and the number of contaminated samples are listed by investigator in Table 2. At the traditional practice site, 6 of 2027 samples were contaminated, yielding a contamination rate of 0.296%. Of the 2030 samples prepared in the cleanroom, 7 were contaminated (0.344%).

A breakdown of contaminated samples by run, investigator, site, and contaminant is displayed in Table 3. Of the positive samples, three were vials and 10 were SVP bags. Fourteen of the 20 runs had no positive results, 3 runs had 1 positive result, 2 runs had 2, and 1 run had 6 positive results. All positive samples were turbid on days 7 and 14.

All 24 of the inoculated positive controls became turbid, indicating contamination. In each case the organism identified by the microbiologist was identical to the one with which the sample was inoculated. None of the negative controls developed turbidity.

Air sampling revealed no viable organisms in either LAF hood. There was an average of 100 CFUs/m^3 in the traditional practice site's surrounding environment and 13 CFUs/m^3 in that of the cleanroom.

Table 4 summarizes the statistical outcomes of this study by dependent and independent variables.

Discussion

Sampling method. This study used simulated product media fills with positive and negative controls as the sampling method. Limitations exist with other available sampling methods. For example, the direct transfer method requires the destruction of the admixture, therefore making large quantity sampling impractical. End-product methods require an additional manipulation, not a natural part of the admixture preparation process, to generate samples. This additional step invites adventitious contamination, leading to falsely high contamination rates. In this study, the results were read

Table 2.
Observed Contamination Rates for Traditional and Cleanroom Environments

Site	Personnel	No. Contaminated Samples/No. Samples Tested			
		Vials	SVP Bags[a]	Total Samples	Total per Site[a]
Traditional	Technician	2/500	3/500	5/1000	6/2027
	Pharmacist	0/514	1/513	1/1027	
Cleanroom	Technician	1/499	5/501	6/1000	7/2030
	Pharmacist	0/515	1/515	1/1030	

[a]SVP = small-volume parenteral.

Table 3.
Contaminated Samples Classified by Run, Investigator, and Site

Run	Investigator	Site	Bag or Vial No.	Organism
1	Pharmacist	Traditional	91	*Corynebacterium* species
2	Pharmacist	Cleanroom	39	*Bacillus* species
2	Technician	Cleanroom	25	Coagulase-negative staphylococci
			14	Coagulase-negative staphylococci
			15	Coagulase-negative staphylococci
			18	Coagulase-negative staphylococci
			21	Coagulase-negative staphylococci
			29	Coagulase-negative staphylococci
2	Technician	Traditional	94	*Corynebacterium* species
			8	Coagulase-negative staphylococci
4	Technician	Traditional	87	Coagulase-negative staphylococci
5	Technician	Traditional	56	Coagulase-negative staphylococci
			46	*Bacillus* species

Table 4.
Statistical Outcomes of Study by Dependent and Independent Variables

Dependent Variables	Independent Variables	*p*[a]
Pharmacist, technician	Cleanroom, vial	0.492
Pharmacist, technician	Traditional site, vial	0.243
Pharmacist, technician	Cleanroom, SVP bag[b]	0.119
Pharmacist, technician	Traditional site, SVP bag	0.368
Traditional site, cleanroom	Pharmacist, technician, vial	1.0
Traditional site, cleanroom	Pharmacist, technician, SVP bag	0.753
Traditional site, cleanroom	Technician, vial	1.0
Traditional site, cleanroom	Technician, SVP bag	0.725
Traditional site, cleanroom	Pharmacist, vial	NA
Traditional site, cleanroom	Pharmacist, SVP bag	1.0
Traditional site, cleanroom	Pharmacist, vial, SVP bag	1.0
Traditional site, cleanroom	Technician, vial, SVP bag	1.0
Vial, SVP bag	Pharmacist, technician, cleanroom, traditional site	0.092
Traditional site, cleanroom	Pharmacist, technician, vial, SVP bag	1.0
Pharmacist, technician	Cleanroom, traditional site, vial, SVP bag	0.012

[a]Fisher's exact test.
[b]SVP = small-volume parenteral, NA = not applicable.

directly from the final container in simulated product media fills. The operator was the only person who had an opportunity to introduce contamination into the sample. The use of this method removed adventitious contamination as a variable affecting the study, produced a large number of samples, and permitted a study of process rather than product.

Media fills were prepared from components used in actual practice to authenticate this study. For example, PVC bags were used instead of glass bottles to simulate the diluent component because bags of sterile water for injection are normally used in the admixture process and there are subtle differences in the manipulation of bags versus bottles. Of the 75 1-L bags prepared for this study, 64 were used. None of the 75 bags became turbid after incubation, indicating that all of the study samples

were prepared with sterile TSB. The remaining components (vials, SVP bags, multiple additive sets, syringes, and needles) are commonly used in the normal admixture process and are available from the manufacturers presterilized.

All 24 positive controls became turbid. In each case, the organism identified after incubation was the same organism originally inoculated, supporting the validity of the sampling methodology. The positive controls demonstrated the ability of the media to support a low concentration of microbial contamination throughout the entire study period.

The number of samples prepared in this study, 4057 vials and bags, is almost triple the total number of samples prepared in previous contamination studies.[4-19] The number of samples prepared is an important consideration in contamination studies measuring statistical significance, which should have a sample size "large enough to yield a high probability of detecting low incidences of contamination."[21] Runs of 100 sample pairs (100 vials and 100 bags) were chosen because this number is a practical simulation of worst-case conditions within a pharmacy, representing the longest period of time that one would prepare admixtures without a break. The runs took 2.5–3 hours to prepare. The two investigators were aware of the study and that the products they were preparing were being monitored. Any investigator bias that may have been introduced was addressed as part of the study design. The study was designed to compare preparation environments (traditional practice versus cleanroom). In addition, the length of the runs was designed to challenge the investigator's physical abilities and aseptic technique.

The results of this study were analyzed by sample type, vial and SVP bag, and then combined into a total sample. Although the containers differ physically, no significant difference in the contamination rates between the two sample sets (vials versus SVP bags) was found ($p = 0.092$).

Study findings. This study found no significant difference in the contamination rates of simulated product media fills prepared at the traditional practice site versus those prepared in the cleanroom ($p = 1.0$). However, the technician, with five years of experience using aseptic technique, contaminated 11 samples in both areas, while the pharmacist contaminated 2 in both areas ($p = 0.012$). This supports the argument that operator technique is an important factor in the control of microbial contamination.

The importance of good aseptic technique, regardless of the environment, is further illustrated when comparing each investigator's contamination rate by site. No significant difference was found in the technician's or pharmacist's contamination rate between the two sites ($p = 1.0$ for each investigator).

It is reasonable to assume that reducing the microbial load of the surrounding environment would decrease the potential for contamination due to viable airborne particulate matter. The results of this study indicate that this assumption is not accurate. The class 100 LAF hood is designed to protect the critical area from airborne particles through filtration and airflow. A difference in viable particulate matter at the two sites was observed using the air sampler; however, no CFUs were found within either LAF hood.

Another important factor in the contamination potential of the environment is the personnel within the environment. The human body can shed approximately 10,000 CFUs/min.[22] This not only affects the microbial load of the air surrounding the human, but provides a source for contamination by touch. Cleanroom garb (e.g., scrubs, gown) is designed to reduce the amount of personnel shedding that occurs within the environment; however, a plastic gown reduces total shedding by only 60%.[22] Gloves are designed to reduce the likelihood of shedding and touch contamination from microbial flora residing on the skin. Since there was no significant difference in the quality of the final products prepared in the cleanroom and traditional practice sites, any environmental considerations are overshadowed by the importance of the operator's aseptic technique.

The Food and Drug Administration, USP, and professional pharmacy associations have stressed the need for effective quality assurance programs for sterile product compounding. They have also emphasized the use of a controlled environment, such as that provided by cleanroom technology, when preparing sterile admixtures, despite the lack of evidence to suggest that these controlled environments independently improve product quality.

It cannot be assumed that the cleanroom environment and garb will prevent or reduce contamination. This false assumption could breed indifference in the personnel working within cleanrooms, thereby weakening their adherence to aseptic technique. This study demonstrates that when admixtures are prepared within a class 100 LAF hood, the operator becomes the most important variable affecting microbial contamination.

It is dangerous to assume that the use of a cleanroom will independently improve the quality of patient care by eliminating contamination. Once a baseline environmental quality (class 100 LAF hood) is established, admixture quality assurance efforts should focus on other critical factors. Continuous quality assurance of personnel's aseptic technique, including effective monitoring and training for the personnel preparing admixtures, is paramount. The use of media-fill runs to validate personnel, processes, and equipment (e.g., automatic compounding devices or pumps) also en-

sures the quality of sterile products. Finally, the proper functioning of LAF hoods should be established.

Limitations. There are limitations to this study. Only one growth medium was used in this study. TSB is an ideal medium for supporting the growth of aerobic gram-positive and -negative bacteria and fungi. Contamination could occur from sources that do not thrive on TSB, such as anaerobes. Growth media to support anaerobes were not used in order to preserve the study's large sample size.

The significance of this study is relative only to the locations in which it was performed. Traditional practice settings vary widely from pharmacy to pharmacy, although many have a class 100 LAF hood. Cleanrooms also vary, but to a far lesser extent. Different results may have been seen if different locations were used.

Arguments could be made that the two investigators may have introduced bias. However, this is unsubstantiated, as the results of the study show no statistically significant difference in contamination rates for either investigator in either environment.

Conclusion

The most important variable affecting microbial contamination of admixtures was the aseptic technique of personnel, not the environment in which the drugs were compounded.

[a]Remel Laboratories, Lenexa, KS, lot 910115.

References

1. Santell JP, Kamalich RF. National survey of quality assurance activities for pharmacy-prepared sterile products in hospitals and home infusion facilities—1995. *Am J Health-Syst Pharm.* 1996; 53:2591-605.
2. Morris AM, Schneider PJ, Pedersen CA et al. National survey of quality assurance activities for pharmacy compounded sterile preparations. *Am J Health-Syst Pharm.* 2003; 60:2567-76.
3. Pharmaceutical compounding—sterile preparations (general information chapter 797). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: The United States Pharmacopeial Convention, 2004:2350-70.
4. Brier KL, Latiolais CJ, Schneider PJ et al. Effect of laminar air flow and cleanroom dress on contamination rates of intravenous admixture. *Am J Hosp Pharm.* 1981; 38:1144-7.
5. Poretz DM, Guynn JB, Duma RJ et al. Microbial contamination of glass bottle (open-vented) and plastic bag (closed-nonvented) intravenous fluid delivery systems. *Am J Hosp Pharm.* 1974; 31: 726-32.
6. Sanders LH, Mabadeje SA, Avis KE et al. Evaluation of compounding accuracy and aseptic techniques for intravenous admixtures. *Am J Hosp Pharm.* 1978; 35: 531-6.
7. Ezell JR, Godwin HN, Hassanein RN et al. Comparison of videocassette and personal instruction methods for training pharmacy personnel in aseptic technique. *Am J Hosp Pharm.* 1988; 45:2112-7.
8. Mitrano FP, Baptista RJ, Newton DW et al. Microbial contamination potential of solutions in prefilled disposable syringes used with a syringe pump. *Am J Hosp Pharm.* 1986; 43:78-80.
9. Dirks I, Smith FM, Furtado D et al. Method for testing aseptic technique of intravenous admixture personnel. *Am J Hosp Pharm.* 1982; 39:457-9.
10. Morris BG, Avis KE, Bowles GC. Quality control plan for intravenous admixture programs. II: validation of operator technique. *Am J Hosp Pharm.* 1980; 37: 668-72.
11. Allinson RR, Stach PE, Sherrin TP et al. Compounding times and contamination rates associated with the preparation of intravenous admixtures in three types of plastic containers. *Am J Hosp Pharm.* 1979; 36:513-7.
12. Buth JA, Coberly RW, Eckel FM. A practical method of sterility monitoring of IV admixtures and a method of implementing a routine sterility monitoring program. *Drug Intell Clin Pharm.* 1973; 7:276-9.
13. Dees EN, Natsios GA. Contamination of intravenous fluids by bacteria and fungi during preparation and administration. *Am J Hosp Pharm.* 1971; 28: 764-7.
14. Ravin R, Bahr J, Luscomb F et al. Program for bacterial surveillance of intravenous admixtures. *Am J Hosp Pharm.* 1974; 31:340-7.
15. Hanson AL, Shelley RM. Monitoring contamination levels of in-use intravenous solutions using "total sample" techniques. *Am J Hosp Pharm.* 1974; 31:733-5.
16. Arnold TR, Hepler CD. Bacterial contamination of intravenous fluids opened in unsterile air. *Am J Hosp Pharm.* 1971; 28:614-9.
17. Miller WA, Smith GL, Latiolais CJ. A comparative evaluation of compounding costs and contamination rates of intravenous admixture systems. *Drug Intell Clin Pharm.* 1971; 5:51-60.
18. Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-5.
19. Trissel LA, Gentempo RW, Anderson RW et al. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005; 62:285-8.
20. Crawford SY, Narducci WA, Augustine SC. National survey of quality assurance activities for pharmacy-prepared sterile products in hospitals. *Am J Hosp Pharm.* 1991; 48:2398-413.
21. Center for Drugs and Biologics and Office of Regulatory Affairs. Guideline on sterile drug products produced by aseptic processing. Rockville, MD: Food and Drug Administration; 1987 Jun.
22. Vanjare D. New concepts in parenteral manufacturing. *PharmaTimes.* 1989; 21:19-20.