Microbiologic Quality-Control Study for the Purpose of Extending the Use of Transfer Sets on the Automix 3+3 and Micromix Automated Total Nutrient Admixture Compounding Pumps

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ABSTRACT. Background: A quality-control study was undertaken by the departments of pharmacy and microbiology at St. Paul’s Hospital (Vancouver, British Columbia, Canada) to evaluate the microbiologic safety of total nutrition admixtures (TNA) compounded by automated compounding pumps when the use of disposable transfer sets was extended from 1 day to 2 days. This study also evaluates the potential annual cost savings of this extended use. Methods: Transfer sets and unused part containers of ingredients were left to sit overnight on the automated compounders after daily TNA manufacturing before a TNA sample was compounded for culturing. These TNA samples were cultured using a biphasic system consisting of a tryptic soy broth component and an agar slide component. Positive results were subcultured and evaluated. Results: Four bags grew Bacillus species, and 1 bag grew coagulase-negative staphylococci. The potential annual cost savings of this extended use was estimated to be $35,000. Conclusions: The extended use of the disposable transfer sets cannot be instituted at the present time and should be reexamined when the cause(s) of the positive results are identified and corrected. (Journal of Parenteral and Enteral Nutrition 29:118–124, 2005)

St. Paul’s Hospital (SPH) Pharmacy currently uses the Automix 3+3 and Micromix compounding pump supplied by Baxter Corporation (Mississauga, Ontario, Canada) for compounding 3-in-1 parenteral nutrition (PN) fluid or total nutrient admixtures (TNA) in which amino acid, dextrose, lipid emulsion, and other micro-nutrient components are compounded into 1 infusion bag. Both of these pumps are computer controlled and gravimetrically calibrated to deliver the desired amounts of each ingredient into a final TNA bag. The Automix 3+3 is used to deliver large-volume ingredients (lipid, dextrose, amino acid, and sterile water), and the Micromix is used to deliver small-volume ingredients such as electrolytes and trace elements. The manufacturing of TNA is accomplished under aseptic conditions in a horizontal laminar airflow hood by specially trained pharmacy technicians and pharmacists proficient in the operation of the compounding pumps and aseptic technique.

These compounding pumps each deliver their ingredients from source containers (vials or bags) into the final TNA bag through disposable transfer sets consisting of a series of tubes. Currently, these transfer sets are replaced every manufacturing day in accordance with Baxter Corporation’s recommendation. There are currently no studies published to support extending the use of these transfer sets to 2 consecutive manufacturing days.

This study was undertaken to evaluate the microbiologic safety of TNA compounded by automated compounding pumps when the disposable transfer sets are replaced every 2 days. This study will also evaluate the potential costs savings of extending the use of the disposable transfer sets.

MATERIALS AND METHODS

Part A: Microbiological Evaluation of TNA

During this study, the pharmacy continued to replace the transfer sets every manufacturing day. However, at the end of each manufacturing day, the transfer sets remained installed on both compounding pumps, along with all remaining part source ingredient containers until the next manufacturing day. At the beginning of the next manufacturing day, 1 small-volume TNA of 120 mL (adequate to flush through all the tubing of both transfer sets) was compounded through the use of the same transfer sets and remaining part source ingredient containers left over from the previous compounding day. This sample collection time was chosen because it was thought that potential for microbial growth was at its greatest during the period of time when the TNA compounding system remained stagnant. New transfer sets and fresh source ingredient containers were then replaced for the day’s regular TNA manufacturing after the small-volume sample TNA had been compounded.

The hospital laboratory used the Septi-Chek System by Becton, Dickinson and Company (Sparks, MD; see...
Fig. 1), which has been shown to be effective for aliquot culturing of TNA. This is a biphasic culturing system consisting of a tryptic soy broth component and an agar slide system consisting of chocolate, MacConkey, and malt agar slides all integrated in a closed system. After visually inspecting a set of fresh Septi-Chek systems, the laboratory technician inoculated the broth of each Septi-Chek system with 10 mL of the sample TNA and then washed the inoculated broth on to the agar slides by inverting the system. Because this is a closed system, this 2-part process was accomplished with minimal risk of contamination. Six Septi-Chek systems were used per 120-mL sample TNA bag in order to aliquot culture 50% of the total volume (see Fig. 2), as recommended by the United States Pharmacopeia for liquids that cannot effectively be tested using the total volume filtration. These systems were incubated at approximately 35°C and examined and then reinverted at 24, 48, 72, 96, and 120 hours by laboratory personnel. Septi-Chek systems positive for growth were subcultured, and isolates were identified by standard methods.

Testing of these sample small-volume TNAs was done each weekday for a period of approximately 2 months.

Part B: Cost Analysis

The volumes of the unused portions from each source container remaining on both automated compounders were estimated and recorded at the end of each regular TNA manufacturing day. The volumes from each source container used in TNA compounding were also recorded daily.

The cost of the used and unused volumes of source ingredients and the cost of replacing the disposable transfer sets were evaluated over the study period to determine current cost of TNA manufacturing. Then a proposed cost of TNA manufacturing based on replacing transfer sets every 2 days was determined by reducing the current cost of source ingredient wastage and cost of current transfer set replacement by 50%. Results from a 40-day data-collection period were then extrapolated to 365 days to express annual costs and savings.

RESULTS

Part A: Microbiological Evaluation of TNA

A total of 5 sample TNA bags were positive for growth. In each case, 1 of 6 Septi-Chek systems detected the growth, whereas the remaining 5 Septi-Chek systems did not detect growth. Table I is a summary of the positive growth results.

Part B: Cost Analysis

As shown in Table II, SPH currently spends $102,468 on source ingredients annually, from which $25,381 goes toward wastage (ie, source ingredients that are discarded along with transfer sets at the end of each manufacturing day). Source ingredients used in TNA compounding include lipid emulsion, amino acid solution, dextrose solution, sterile water, potassium phosphate solution, magnesium sulfate solution, trace element solution, selenium solution, sodium chloride solution, potassium chloride solution, zinc sulfate solution, calcium gluconate solution, and folic acid solution. The amount of each source ingredient used and wasted varied from day to day as it depended on the quantity and properties of the TNAs ordered each day. It is therefore projected that both the total annual cost of source ingredients and cost of wastage would be reduced to $89,777 and $12,690, respectively, under the proposed extended use of the transfer sets. This cost reduction equates to an annual savings of $12,691 in cost toward source ingredients.

As shown in Table III, the current annual cost of replacing transfers sets is approximately $45,800, according to ~$125 per day for 365 days for the daily replacement of both transfer sets. An annual cost savings was projected at $22,900 by replacing the transfer sets every 2 days. This is based on 50% of the current annual cost or transfer set replacement 183 days per year.

Table IV shows that with the savings in source ingredients and transfer sets, SPH can expect a total annual
Organisms implicated were from blood, catheter tip, sputum, or urine, which PN fluid cultures correlated with positive cultures in the study (25 of 42 organisms cultured). K pneumoniae appeared to be the most predominantly cultured from each type of PN fluid. However, there were no differences in terms of predominant organisms made in terms of predominant organisms cultured in each type of PN fluid. Results from in vitro studies comparing the 2 types of PN fluids are mixed. A report by Scheckelhoff et al. showing no significant differences in growth of bacteria and fungi in TNA compared with dextrose 5% solution over a 48-hour period, whereas Didier et al. showed no differences in rates of PN-related sepsis between the use of conventional PN fluids and TNAs. Vasilakis and Apelgren found that of the 200 samples examined, 17% tested positive for microbes (conventional: 15 of 88 samples; TNAs: 19 of 112 samples). Organisms isolated included Staphylococcus epidermidis, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas multocida, Proteus mirabilis, Acinetobacter, diphtheroids, Bacillus species, Candida parapsiloides, and Candida albicans. There were no distinctions made in terms of predominant organisms cultured from each type of PN fluid. However, S epidermidis appeared to be the most predominately cultured organism in the study (25 of 42 organisms cultured). Clinically, 6 of 49 patients developed sepsis in which PN fluid cultures correlated with positive cultures from blood, catheter tip, sputum, or urine. Organisms implicated were S epidermidis, P mirabilis, K pneumoniae, and C parapsiloides. However, 18 of 49 patients remained clinically well in spite of positive cultures from their PN fluid. A study by Llop et al. revealed that 10 of 69 TNA samples tested positive for S saprophyticus. As a result, 4 of 45 patients developed sepsis, only 2 of which were confirmed with positive blood cultures for the organism. Another investigation by Verschraegen et al. reported an outbreak of Enterobacter cloacae septicemia in 5 surgical patients receiving TNA that later tested positive for the same organism. In this case, the author had traced this contamination to the breaches in the pharmacy production line. All these studies seem to show some correlation of clinical sepsis with TNA contamination.

On the other hand, there are also studies that suggest there is no correlation between TNA contamination with clinical sepsis. Dolin et al. cultured 96 TNA bags from 23 patients in which 4 TNA bags had positive cultures. The organisms cultured included S epidermidis, Streptococcus viridins, and Bacillus species. In the course of the study, 2 patients developed sepsis in which blood cultures could not be correlated with a positive culture in a TNA bag. As well, Montego et al. cultured 1294 TNA bags in which 59 bags were positive for S epidermidis and E cloacae. However, except for 2 bags which were confirmed to have grown E cloacae, the rest were deemed false positive because of external contamination during sampling. Although it was not included in the results, the discussion of this study did mention that during the course of the study, patients who developed sepsis could not be correlated to contaminated TNA bags.

The results of this study showed that 5 of 40 TNA test bags had possible microbial growth. Because only 1 of 6 Septi-Chek systems was positive for growth in each case, the level of contamination is either very low in the bags or the result may have been a false positive because of mishandling of the final product. Four bags were positive for Bacillus species, and the fifth bag grew coagulase-negative staphylococci. The Bacillus species is normally found in soil and dust, whereas the coagulase-negative staphylococci are usually associated with touch or surface contamination. The results of this study were unexpected as the use aseptic technique in an aseptic environment theoretically should have minimized any chances of microbes being introduced during the manufacturing process, regardless of how long the transfer sets have been left idle.

The pharmacy and the laboratory were both considered as potential sources of the positive results. Faulty

### TABLE I
Summary of positive growth results

<table>
<thead>
<tr>
<th>Bag no.</th>
<th>Positive Septi-Chek systems</th>
<th>Colonies</th>
<th>Organism ID</th>
<th>Time examined, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>1 of 6</td>
<td>1</td>
<td>Bacillus coagulans</td>
<td>120</td>
</tr>
<tr>
<td>17</td>
<td>1 of 6</td>
<td>&gt;100</td>
<td>Bacillus coagulans</td>
<td>96</td>
</tr>
<tr>
<td>23</td>
<td>1 of 6</td>
<td>50</td>
<td>Bacillus sphaericus</td>
<td>72</td>
</tr>
<tr>
<td>28</td>
<td>1 of 6</td>
<td>Overgrowth</td>
<td>Coagulase-negative staphylococci</td>
<td>120</td>
</tr>
<tr>
<td>40</td>
<td>1 of 6</td>
<td>&gt;100</td>
<td>Bacillus megaterium</td>
<td>48</td>
</tr>
</tbody>
</table>

*Total positives for growth, 5 of 40 bags.

### TABLE II
Cost analysis of source ingredients

<table>
<thead>
<tr>
<th>Current Cost, $</th>
<th>Proposed Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost</td>
<td>Total cost in waste</td>
</tr>
<tr>
<td>$102,468</td>
<td>$25,381</td>
</tr>
</tbody>
</table>

*Savings: $12,691.

### TABLE III
Cost analysis of transfer sets replacements

<table>
<thead>
<tr>
<th>Current cost</th>
<th>Proposed cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>$45,800</td>
<td>$22,900</td>
</tr>
</tbody>
</table>

*Savings: $22,900.
Septi-Chek systems, source ingredient contamination, touch or surface contamination, and environmental contamination were all explored as possible problematic areas.

The use of faulty Septi-Chek culturing systems may possibly have given us false-positive results. However, the Septi-Chek systems used in this study were all visually inspected before inoculation by laboratory personnel and were not part of any batches on recall by the manufacturer. Therefore, false-positive results from the use of faulty Septi-Chek systems are highly unlikely.

Inherent source ingredient contamination is also another possibility that was considered in our evaluation. All source ingredients used in TNA manufacturing are preservative free and are deemed sterile by the manufacturer. To our knowledge, there have not been any defects or recalls put out by the manufacturers. However, there is always the possibility of low-level contamination that may have been overlooked by the manufacturers’ quality-assurance evaluations. We consider this possibility to be highly unlikely.

Touch or surface contamination was also considered during the evaluation of the results. Coagulase-negative staphylococcus has traditionally been associated with this type of contamination. The 1 positive result that grew this organism may therefore have been caused by technique. Pharmacy technicians and laboratory personnel are trained to exercise validated aseptic techniques in the preparation and handling of microbiologically sensitive preparations. However, there is a possibility of momentary breach in aseptic technique because of human error. Whether this occurred in the TNA room or the laboratory remains unknown. We can only conclude that there was a possibility that this positive result may have been related to touch or surface contamination.

The environmental conditions of our pharmacy TNA manufacturing room were considered to be a major potential source of our positive results.

TNA manufactured by automated compounders is classified as a risk-level 2 product by guidelines set out by the American Society of Health System Pharmacists (ASHP). ASHP guidelines recommend that risk-level 2 products be manufactured using aseptic technique in a class 100 (≤100 particles of 0.5-µm size or larger per cubic foot of air) environment that may be in the form of a certified laminar airflow workbench, a class 100 clean room, or a barrier isolator. As in this case where a certified laminar airflow workbench is used, it is recommended that the unit be situated in a room that meets class 10,000 (≤10,000 particles of 0.5-µm size or larger per cubic foot of air) clean room standards and also maintains a positive air pressure relative to the adjacent pharmacy areas.

Information provided by the chief engineer from SPH physical plant department indicates that air supplied to the hospital is filtered. The final filters are 95% efficient and the prefilters are 30% efficient. The air supplied to the main pharmacy sterile room is a mixture of outside and recirculated air. The mixture of outside and recirculated air is dependent on the outside temperature. As verified by studying the airflow patterns through the door jambs of the room entrances, the sterile room also exerts a positive pressure in relation to the adjacent pharmacy areas, as recommended by ASHP guidelines.

However, air quality in the sterile room has not been tested for particulate or microbial matter and therefore does not bear an official clean room class, as recommended by the ASHP guidelines. The existing compounding area is part of an open-architecture design with relatively unrestricted access by pharmacy staff members, which makes it difficult to maintain air quality. ASHP guidelines recommend that TNA compounding take place in a controlled area separated from the rest of the pharmacy sterile room by a barrier (eg, plastic curtain or partition wall), with entry limited only to appropriately garbed personnel for the sole purpose of operating the TNA compounders. As well, the existing sterile room has many surfaces (shelves, carts, countertops) that allow the accumulation of dust and other particulate matter. To date, a cleaning and disinfecting protocol for these surfaces as outlined in the ASHP guidelines has not been adopted into the operation of the SPH pharmacy sterile room.

Laminar airflow hoods (LAFHs) are designed to minimize the probability of contamination of sterile products by providing a constant flow of filtered air that sweeps the critical area to prevent entry of contaminated room air. These systems typically consist of a motorized air blower, prefilter, and a high-efficiency particulate air (HEPA) filter. The air blower draws air into the LAFH from the room or exterior environment through the filters and out over the critical area of the unit. The prefilter removes gross contaminants such as dust or lint, and the HEPA filter removes 99.9% of all 0.3-µm or larger particles such as bacteria, pollen, and dust. The combination of the constant airflow provided by the air blower and the filtration provided by the dual filter system creates the class 100 conditions in the critical area.

There are several types of LAFH systems available, and each is designed for specific applications. TNA manufacturing is done in a horizontal LAFH in which the laminar airflow is directed toward the worker and the room. This type of LAFH provides no protection to the worker if hazardous materials were to be handled inside the hood; however, these units are easily relocatable as they do not need venting to outside air.

The placement requirements of objects in the horizontal LAFH are a significant limitation to our applications. Objects placed in the hood disrupt the airflow by causing turbulence in front of and behind the object. Spaces within the airflow disruptions are less protected from contamination. This airflow disruption is normally about 2.5 times the diameter of the object. As well, positions downstream of objects are not only
areas of turbulent airflow but also susceptible to contamination from the surface of objects carried by the airstream. The airflow is also susceptible to turbulence a short distance into the hood, caused by rebound airflow off the worker. Therefore, it is recommended that critical operations be performed at least 15 cm within the hood to minimize contamination from this effect.16

The horizontal LAFH in this facility undergoes annual assessment of its operation by the University of British Columbia’s department of biosafety. This evaluation includes a filter-leak test, smoke-pattern test, supply-velocity test, and an average-intake-velocity test. However, these tests are only limited to the evaluation of the operation of the horizontal LAFH with no placement of objects in the critical areas. Therefore, this certification does not give any indication of the performance of the horizontal LAFH in our applications.

As one can observe from Figure 3, the TNA manufacturing setup at SPH is less than ideal for the efficient performance of the horizontal LAFH. The size of the compounders themselves results in large areas of air turbulence, which potentially affects the areas in which critical sites are located. These critical sites include TNA bag entry points and source ingredient container entry points. As well, the size of the compounders limits their ability to be placed such that the critical sites are within the recommended 15 cm from the edge of the hood area (see Fig. 4). This limitation, in combination with frequently having a worker situated in front of the LAFH as required by the manufacturing process, and airflow disturbances caused by movement of workers place critical areas at risk of rebound turbulence.

Brier et al17 did a study to determine the effect of laminar airflow and clean-room dress on microbiologic contamination rate of IV admixture products. Clean-room dress was defined as clean coat, sterile gloves, foot cover, mask, and hair cap. Three hundred fifty IV admixtures were compounded in each of the 4 conditions: laminar airflow with and without clean-room dress and clean tabletop with and without clean-room dress. In the laminar airflow tier, 1 of 350 was positive for growth (Bacillus species) with clean-room dress and 1 of 350 was positive for growth (anaerobic diphtheroid) without clean-room dress. In the clean tabletop tier, 4 of 350 were positive for growth (S epidermidis) with clean-room dress and 5 of 350 were positive for growth (S epidermidis and Bacillus species) without clean-room dress. The author concluded that IV admixture compounding under laminar airflow significantly decreased the rate of contamination, whereas the use of clean-room dress did not significantly affect contamination rates. As for the SPH pharmacy, the results of this study may potentially be extrapolated to contamination caused by ineffective laminar airflow during the TNA compounding process. However, we must keep in mind that environmental conditions in this study may not be equal to the conditions at the SPH pharmacy.

A secondary investigation was done to assess whether there was any correlation between the performance of the flow hood and the results of this study. This secondary investigation involved placing fresh blood agar plates near the critical sites of the LAFH during the daily manufacturing period for 5 consecutive days. These blood agar plates were then incubated over 5 days by the hospital laboratory and assessed for microbial growth. Two plates from the same area of the LAFH, but situated on different days, resulted positive for microbial growth. One plate grew 1 colony of a fungus species, and the other plate grew 2 colonies of a Staphylococcus species and 1 colony of a Micrococcus species. Though this investigation was very brief and not powered to reflect statistical significance, the organisms that grew did not correlate with the organisms grown in the study. However, the fact that this investigation resulted in positive growth may indicate that the setup in the LAFH may need reevaluation.
Because the laboratory was also considered as a possible source of contamination during the analysis phase of the study, a similar investigation was also performed in their LAFH. The laboratory uses a type of LAFH classified as a biologic safety cabinet in which the laminar air flows in a vertical direction (top to bottom) and the worker is protected from any harmful substances by a glass barrier. This investigation resulted in positive growth for diphtheroids, Streptococcus viridans, and Micrococcus species. Again, the organisms grown appeared not to correlate with the organisms grown in the study.

Nonetheless, the results from this secondary investigation were interesting in that many of the organisms that grew on the plates were listed by Dolin et al as sampling contaminants during their study. They defined sampling contamination as growth that occurred on the agar plates but not in the broth media from which the agar plates were subcultured. They had attributed contamination of their agar plates from the laboratory environment or from laboratory manipulation. Their list of organisms included Staphylococcus species, micrococci, fungus, Bacillus species, diphtheroids, and Acinetobacter. Again, caution should be exercised when extrapolating this data to the results of this study’s secondary investigation because the conditions that fostered the contamination may not be equal.

We do not consider the positive results presented in this study to be a direct cause from the unendorsed simulated extended use of the transfer sets itself. In order for contamination to take place, there must first be an opportunity for microbes to enter the bags. Again, the use of aseptic technique in an aseptic environment during TNA manufacturing should have prevented this from occurring. This may be an indication of possible deficiencies in our TNA manufacturing room setup or in our technique. Of course, we must also consider that some of these may be false-positive results from touch contamination of the end product or contamination during the culturing phase of the study.

Though many factors have been discussed as possible causes of the contamination, we consider the TNA room setup to be one of the highest probable contributors, and thus a logical starting point for possible correction. At first glance, the size of the horizontal LAFH the department is currently using does not allow the critical sites of the Micromix compounder to be within the 15-cm limit from the edge of the workbench, hence putting those critical sites in less-protective rebound turbulent airflow (see Fig. 4). Second, we consider the size and design of the actual compounders to be a major limiting factor in the performance of any size horizontal LAFH. Though airflow studies have not been formally conducted, it appears that the design of the compounders does not allow nonturbulent laminar airflow to adequately sweep and protect the critical sites (ie, source container entry points) of the compounder. Third, even though air entering the TNA manufacturing room is filtered, there has not been a formal air-quality test to confirm that the room meets class 10,000 standards. This is especially important as traffic in and out of the room by pharmacy personnel is relatively liberal and frequent, which may potentially compromise the room air quality.

The design of this study is limited by a small sample size that is not powered for statistical significance. This study lacks a control to rule out false-positive results, as well as a comparison control test bag compounded immediately after the daily TNA manufacturing before leaving the transfer sets to sit idle for the night. As well, a study of this type should also include a clinical component that explores rates of sepsis in the hospital as related to TNA contamination. This study serves as an informative pilot study to set the groundwork for future larger studies.

CONCLUSIONS

Even though the studies reviewed in the discussion show conflicting results with regard to the correlation between PN fluid contamination and clinical sepsis, we cannot ethically institute the extended use of these transfer sets with the knowledge of positive microbial growth in this study. However, the potential annual cost savings of approximately $35,000 as projected in this study stands to be a strong motivator to correct any deficiencies that may be the culprit for the positive results. Therefore, these deficiencies should be explored and corrected before further studies of this type are repeated. The following recommendations numbered from 1 to 8 are intended to facilitate the SPH TNA compounding area to correct its deficiencies and to meet ASHP standards for compounding of risk-level 2 sterile products.7

1. Replace the existing LAFH with an adequately sized LAFH to allow the critical sites of the automated compounders to be within the recommended 15-cm distance from the edge of the LAFH work surface.
2. Initiate a disinfection protocol for all surfaces prone to dust accumulation. Critical-area work surfaces such as the interior of the LAFH should be disinfected at least daily. Floors should be disinfected at least daily. Surfaces including but not limited to shelves, carts, countertops, and stools should be disinfected at least weekly. Walls should be disinfected at least monthly.
3. Reinforce handwashing with an antibacterial soap and ensure the use of proper gloves (disinfected with 70% isopropyl alcohol immediately before direct contact with objects within the critical areas), gowns, masks, and hairnets by personnel in direct operation of the automated compounders.
4. Designate the TNA compounding area as a controlled area by constructing a barrier separating its airflow from the airflow of the rest of the sterile room.
5. Restrict the entry into the controlled area only to personnel who are appropriately garbed (recommendation 3) and whose purpose of entry is solely to operate the automated compounders or related activities.
6. If recommendation 4 is not possible, entry into the existing sterile room should be restricted to personnel who are appropriately garbed (recommendation...
3 ± gloves) and have reason for entry into the sterile room.
7. Ensure that the sterile room or the controlled areas are certified to meet class 10,000 clean-room standards.
8. Initiate scheduled monitoring of airborne microbial contamination in the sterile room or the controlled areas and critical areas (interior of the LAFH) with the use of settle plates or surface-wipe samples.

ACKNOWLEDGMENTS
The study was funded by the Departments of Microbiology and Pharmacy, St. Paul’s Hospital. Special thanks to Dr. Alison Clarke, MB, FRCP(C), Department of Microbiology, St. Paul’s Hospital, for her expert advice and review of this manuscript; to Ms. Anna Wong, Department of Microbiology, St. Paul’s Hospital, for processing the microbiologic samples and filling out the piles of paperwork; to Dr. Stephen Shalansky, PharmD, Department of Pharmacy, St. Paul’s Hospital, for review of this manuscript; to all the staff in the Department of Pharmacy, St. Paul’s Hospital, for their unrelenting support and for compounding the TNA samples in such a timely fashion; and to Dave Rutledge, Chief Engineer, Physical Plant Department, St. Paul’s Hospital, for providing the information on the airflow properties in the pharmacy sterile room.

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