Maximizing the Use of Single-Dose Vials

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Clinical IQ, LLC
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Disclaimer

“Although I am a member of the USP Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.”
Special Thanks and Acknowledgement

Some slides in this presentation were provided by:

- John W. Metcalfe, Ph.D., Senior Review Microbiologist, FDA/CDER/OPS/New Drug Microbiology Staff
  - John presented at PDA’s 6th Annual Global Conference on Pharmaceutical Microbiology, October 17, 2011

- Kathleen Meehan Arias, MS, MT(ASCP), CIC, Arias Infection Control Consulting, LLC
  - Kathleen presented during Pharmacy OneSource’s webinar titled: “Outbreaks Associated with Unsafe Injection and Medication Practices and How We Can Prevent Them”, June 20, 2012

- Michael R. Cohen, RPh, MS, ScD, FASHP-Institute for Safe Medication Practice (ISMP).
US SURGEON GENERAL’S WARNING:
This presentation contains professional language, professional content, and psychological nudity.
Attendee discretion is advised.
What is the issue?

• The US has been experiencing a growing problem of drug shortages
• Most drugs come in single-dose vials (SDVs) and typically contain more drug than one dose
• The cost of discarding the remaining drug in a SDV can total upwards to $750,000 annually, especially for hazardous drugs
• Improper use of SDVs has resulted in events of nosocomial infections and patient deaths
• ASHP, CDC, CMS, FDA, ISMP and the USP have all weighed in on this issue
• Strict compliance with USP 797 provides a solution to ease the drug shortage by permitting the repackaging on medications from SDVs
National Drug Shortages

January 1, 2001 - November 30, 2011

Note: Each column represents # of new shortages identified during that year
University of Utah Drug Information Service
Shortages by Drug Class

<table>
<thead>
<tr>
<th>Category</th>
<th>2011 11/30/11</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Autonomic</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>CNS</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>EENT</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Hormone</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

University of Utah Drug Information Service
Form Type

- Injectables: 82%
- Orals: 15%
- Inserts/Implants: 1%
- Rectals, Topical: 1%
- Dermatologica1: 1%

Brand-Generic Type

- Generic: 83%
- Brand: 11%
- Branded Generic: 2%
- Other-Branded Generic: 4%

Source: IMS National Sales Perspectives, Sep 2006 – Aug 2011
Therapy Area: % of Products

- Oncology: 16%
- Anti-infectives: 15%
- Cardiovascular: 12%
- Central Nervous System: 11%
- Pain: 9%
- Vitamins, Minerals: 9%
- Other: 28%

Source: IMS National Sales Perspectives, Sep 2006 – Aug 2011
Pain Points

• Deployment of finite resources (operational and clinical) to blunt patient impact of drug shortages
• Delays or postpones patient care/treatment because of lack of drug
• Adverse patient care events because of medication errors
• Greater potential for organizational liability associated with critical drugs acquired through parallel market
• Financial impact of purchasing shortage drugs
• Lowering safety standards will not address the problem of drug shortages. –CDC Single-dose/Single-use Vial Position& Messages, April 27, 2012
Definition of SDVs

USP-General Notices

• 10.20.60. Single-Unit Container

  – A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

• 10.20.70. Single-Dose Container

  – A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled. (See also Containers for Injections under Injections 1.)
Definition of SDVs

• FDA
  – **Vial, Single-Dose:** A vial containing a single unit of a parenteral drug product.
  – **Vial, Single-Use:** A vial where a single dose of a parenteral drug product can be removed and then the vial and its remaining contents can be disposed.

• CDC
  – **A single-dose or single-use vial:** is a vial of liquid medication intended for parenteral administration (injection or infusion) that is meant for use in a single patient for a single case/procedure/injection. Single-dose or single-use vials are labeled as such by the manufacturer and typically lack an antimicrobial preservative.
CDC Single-dose/Single-use Vial Position

- Issued on April 27, 2012 to restate its position on the use of these vials and seeks to dispel inaccuracies being disseminated to healthcare providers.

- CDC guideline call for medications labeled as “single dose” or single use to be used for only one patient.

- Intended to protect patients from life-threatening infections when vials become contaminated from unsafe injection practices—include, but are not limited to, reuse of syringes for multiple patients or to access shared medications, administration of medication from a single-dose/single-use vial to multiple patients, and failure to use aseptic technique when preparing and administering injections.

- CDC Injection safety guidelines are not new. They have been part of Standard Precautions since 2007.

http://www.cdc.gov/injectionsafety/IP07_standardPrecaution.html
In certain instances, qualified healthcare personnel may repackage medication from a previously unopened single-dose/single-use vial into multiple single-use vehicles (e.g., syringes). This should only be performed under ISO Class 5 conditions in accordance with all standards in by the United States Pharmacopeia General Chapter 797, Pharmaceutical Compounding – Sterile Preparations, as well as the manufacturer’s recommendations pertaining to safe storage of that medication outside of its original container.

In 2002, an informal communication to the Centers for Medicare and Medicaid Services (CMS) suggested that certain medications packaged in a single-dose/single-use vial could be used for more than one patient in dialysis settings, assuming that certain criteria were followed. In 2008, CDC issued a formal clarification specifically to dialysis providers stating that the 2007 guidance superseded the 2002 CDC communication to CMS.
Single-dose Vials: Safe Practices

• Use single-dose medication vials, pre-filled syringes and ampoules when possible

• Do not administer medications from single-dose vials or ampoules to multiple patients

• Do not combine leftover contents for later use

• Store vials in accordance with manufacturer's recommendations and discard if sterility compromised or questionable

HICPAC Guideline for Isolation Precautions, 2007
SDVs and CMS


  – Under certain conditions, it is permissible to repackage single-dose vials or single use vials (collectively referred to in this memorandum as “SDVs”) into smaller doses, each intended for a single patient.

  – Administering drugs from one SDV to multiple patients without adhering to USP <797> standards is not acceptable under CMS infection control regulations
"Unfortunately, there are too many in health care who feel that if it hasn't happened to them, the adverse experiences of others do not apply. “

Michael Cohen, MS, FASHP
Institute for Safe Medication Practices (ISMP)
Brutal Facts

Nosocomial Infections-Microbial Contamination Following CSP Preparation

  – 62 cases of infectious disease.
  – 7 different hospitals.

  – “To prevent further outbreaks, the people administering the agents must fully understand the ability of these drugs to support microbial growth so as not to put the patients at risk.”

Scenario
- Received IV ranitidine compounded with ACD while in the hospital.
- Multidose source vial hung for 48 hours on ACD

Action/Results
- 3 patients successfully treated
- 1 patient developed meningitis and transferred to another hospital

Root Cause
- Inadequate hand-washing
- Noncompliance with garbing requirements (ASHP Guidelines-Risk Level 2)
Brutal Facts

Maryland, December 2004


- Scenario
  - Sixteen (16) patients from three (3) clinics develop HCV infection after administration of Tc 99m radioisotope used in cardiac stress tests
  - Contamination implicated to be a cross-contamination between a blood-labeling procedure and the preparation of the radioisotope
  - Sixteen patients contract Hepatitis C: Several patients adversely affected (death and disease)

- Root Cause
  - Breaks in aseptic technique were identified at the pharmacy. SDV of saline was shared during aseptic procedures. Nuclear pharmacies that handle biological products should follow appropriate aseptic technique to prevent contamination of sterile radiopharmaceuticals.

2 women (60 and 77 yrs) diagnosed with acute hepatitis B; both received chemotherapy at same physician's office

Health care-associated transmission suspected

Investigation:
  - 2,700 patients notified
  - 29 HBV cases identified
Brutal Facts

New Jersey, 2009 (continued)

• CAUSE?
  – Common-use saline bags
  – Reuse of single-dose vials
  – Poor hand hygiene
  – Meds prepared in blood processing area

• Results:
  – Office practice was closed
  – Physician's license suspended
Brutal Facts

Florida, August 2011

• August 2011, Contaminated Avastin Syringes-FDA Drug Safety and Availability (http://www.fda.gov/Drugs/DrugSafety/ucm270296.htm)

• FDA Alerts Health Care Professionals of Infection Risk from Repackaged Avastin Intravitreal Injections

• The Florida Department of Health (DOH) notified FDA of a cluster of *Streptococcus endophthalmitis* infections in three clinics following intravitreal injection of repackaged Avastin.

• Investigators traced the tainted injections to a single pharmacy located in Hollywood, Florida.

• The pharmacy repackaged the Avastin from sterile injectable 100 mg/4 mL, single-use, preservative-free vials into individual 1 mL single-use syringes.
Brutal Facts

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

TO: Michel (Paul) Rino, Director of Pharmacy & Owner
FIRM NAME: Infapharm, LLC
CITY, STATE AND ZIP CODE: Hollywood, FL 33020
TYPE OF ESTABLISHMENT INSPECTED: Compounding Pharmacy

DATES OF INSPECTION: 7/18-7/22/11, 9/16-23/11 & 5/27/11
FE-NUMBER: 309802549

This document lists observations made by the FDA representatives during the inspection of your facility. These observations do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement corrective action in response to an observation, you may discuss the objection or action with the FDA representatives during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

During an inspection of your facility, the FDA observed:

1. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written or followed. Specifically:

   a) There was a failure to handle and store components and drug products at all times in a manner to prevent contamination. For example, between 9/23/10 and 7/11/11, single-use vials of Avastin® (bevacizumab) solution for intravenous infusion were frequently used as multiple-use vials during your firm's repackaging operations into individual syringes for intravenous injection without taking into consideration the microbiological, physical and chemical stability of the opened vial of Avastin® after the initial puncture. According to the package insert for Avastin®, after opening the vial the manufacturer recommends to “discard any unused portion left in a vial, as the product contains no preservatives.” However, your firm conducted the following repacking operations that were not in accordance with the manufacturer’s recommendations for this drug product:

      1. As per your statement on 7/19/11, two (2) vials of Avastin® 4 mL were received by your firm and were repackaged into 0.1 mL syringes on multiple days as follows:

         i) Lot 06212011 repackaged on 6/21/11: 16 syringes
         ii) Lot 07012011 repackaged on 7/11/11: 4 syringes
         iii) Lot 07052011 repackaged on 7/15/11: 30 syringes
         iv) Lot 07062011 repackaged on 7/17/11: 15 syringes

      These batches of repacked Avastin® have been associated with twelve (12) reports of bacterial infections of the eye after intravenous administration.

Brutal Facts

Arizona and Delaware; 2012

- CDC MMWR, Vol. 61, No.27 July 13, 2012. Invasive Staphylococcus aureus Infections Associated with Pain Injections and Reuse of Single-Dose Vials

- This report summarizes the investigation of two outbreaks of invasive Staphylococcus aureus infection confirmed in 10 patients being treated for pain in outpatient clinics.

- In both investigations, clinicians reported difficulty obtaining the medication type or vial size that best fit their procedural needs.

- If SDVs must be used for more than one patient, full adherence to U.S. Pharmacopeia standards is critical to minimize the risks of multi-patient use.

- Since 2007, the year that injection safety was included as part of Standard Precautions, 20 outbreaks associated with use of single-dose or single-use medications for more than one patient have been reported (CDC, unpublished data, 2012).
<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Clinical Syndrome</th>
<th>Medication</th>
<th>Intrinsic or Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteria</td>
<td>PR</td>
<td>Heparinized saline</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Acinetobacter calcoaceticus</td>
<td>Peritonitis</td>
<td>Peritoneal dialysate</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>BSI</td>
<td>Sterile water</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Enterobacter cloaceae</td>
<td>BSI</td>
<td>Multidose dextrose</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>RTI</td>
<td>Albuterol</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>BSI</td>
<td>Fentanyl</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Ralstonia picketti</td>
<td>BSI</td>
<td>Human albumin</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Serratia marcesens</td>
<td>BSI</td>
<td>Multidose dextrose</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Serratia liquefaciens</td>
<td>BSI</td>
<td>Parenteral nutrition</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Serratia odorifera</td>
<td>UTI, colonization</td>
<td>Ultrasound coupling gel</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Mixed gram-negative</td>
<td>BSI</td>
<td>Multidose dextrose</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>BSI</td>
<td>Sterile water, injection</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>BSI</td>
<td>Fentanyl</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>RTI/colonization</td>
<td>Sterile saline, respiratory</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>BSI, PR</td>
<td>Fentanyl</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td></td>
<td>Epoetin alfa</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>BSI</td>
<td>Parenteral nutrition</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Mycobacterium abscessus</td>
<td>BSI</td>
<td>Parenteral nutrition</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Mycobacterium chelonae</td>
<td>BSI</td>
<td>Calcium gluconate</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Fungi</td>
<td>Abcesses</td>
<td>DTP vaccine</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>BSI</td>
<td>Parenteral nutrition</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>Abcesses</td>
<td>DTP vaccine</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Virus</td>
<td>Abcesses</td>
<td>Adrenal cortical extract</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>HIV</td>
<td>Abcesses</td>
<td>Multidose lidocaine</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>HBV</td>
<td>Abcesses</td>
<td>Parenteral nutrition</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>HCV</td>
<td>BSI, disseminated</td>
<td>Parenteral nutrition</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Multiple organisms</td>
<td>Endophthalmitis</td>
<td>Balanced salt solution</td>
<td>Intrinsic</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Transmission</td>
<td>Hemodialysis flush solution</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Gram-positive toxins</td>
<td>Transmission</td>
<td>Multidose saline</td>
<td>Extrinsic</td>
</tr>
<tr>
<td></td>
<td>Transmission</td>
<td>Multidose local anesthetic</td>
<td>Extrinsic</td>
</tr>
<tr>
<td></td>
<td>Transmission</td>
<td>Multidose saline</td>
<td>Extrinsic</td>
</tr>
<tr>
<td></td>
<td>BSI, SSI, fever</td>
<td>Propofol</td>
<td>Extrinsic</td>
</tr>
<tr>
<td></td>
<td>Sterile peritonitis</td>
<td>Peritoneal dialysate</td>
<td>Intrinsic</td>
</tr>
<tr>
<td></td>
<td>Fever/hypotension</td>
<td>Polygeline</td>
<td>Intrinsic</td>
</tr>
</tbody>
</table>

Abbreviations: PR, pyrogenic reaction; BSI, bloodstream infection; RTI, respiratory tract infection; UTI, urinary tract infection; DTP diphtheria-tetanus-pertussis; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; SSI, surgical site infection. Seminars in Infection Control. vol. 1, no. 2, June 2001
It’s about contamination & preventing it, STUPID!
USP 797 and SDVs/MDVs

Single/Multiple Dose Vials

• Definitions of SDV and MDV are in the USP General Notices and Requirements

• Single dose vials – Opened or punctured in ISO 5 environment may be used for up to 6 hours. Opened or punctured in worse than ISO 5 must be used within 1 hour or discarded.

• Single dose ampoules must be discarded after opening and not stored for any time period
# Calculated Microbial Growth

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Microbial Count (CFU per mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>640</td>
</tr>
<tr>
<td>12</td>
<td>41,000</td>
</tr>
<tr>
<td>18</td>
<td>$1.7 \times 10^7$</td>
</tr>
<tr>
<td>24</td>
<td>$6.9 \times 10^9$</td>
</tr>
</tbody>
</table>

Cundell AM, USP Committee on Analytical Microbiology, Pharmacopeial Forum 2002; 28 (6) Stimuli to the Revision Process
Drug Vial Optimization Studies

• Purpose to show that sterility of the vial is maintained. Results should demonstrate 0% growth

• The use of a CSTD (PhaSeal™) has been claimed to extend the life of a SDV

• Two studies (one unpublished) reported a contamination rate of 1.8%*
  
  – Contamination was attributed to poor aseptic technique used when plating the media
  
  – There was no control group (media fills without the use of a CSTD)


Drug Vial Optimization Studies
(continued)

• De Prijck, et al\(^\dagger\), noted:
  – PhaSeal “had the lowest transfer of microorganisms”
  – The study demonstrated a 2.2% to 2.5% contamination rate with PhaSeal
  – Noted that the level of contamination was dependent on the number of couplings.
  – De Prijck and his coauthors note:
    that the use of high inoculum used in the study should be considered in context of their results as well as the need for a robust disinfection step

# Microbiological Growth

## Table 1: Non-Nutritional Parenteral Solution Microbe Viability

<table>
<thead>
<tr>
<th>Drug/Solution</th>
<th>Conc. (mg/mL)</th>
<th>S. aureus</th>
<th>E. faecium</th>
<th>P. aeruginosa</th>
<th>C. albicans</th>
<th>B. subtilis</th>
<th>E. coli</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>50.00</td>
<td>IMG</td>
<td>IMG</td>
<td>IMG</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>6, 7</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>0.03</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
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<tr>
<td>Bendamustine HCl</td>
<td>0.25</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>5</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.00</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
</tr>
<tr>
<td>Basulfan</td>
<td>0.50</td>
<td>IMG</td>
<td>IMG</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
</tr>
<tr>
<td>Basulfan</td>
<td>6.00</td>
<td>IMG</td>
<td>IMG</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
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<td>Cetuximab</td>
<td>2.00</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1.00</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>6, 7</td>
</tr>
<tr>
<td>Cladribine</td>
<td>0.03</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>5</td>
</tr>
<tr>
<td>Cytarabine</td>
<td></td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>6</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0.80</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>5</td>
</tr>
<tr>
<td>Doxorubicin (Liposomal)</td>
<td>0.15</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>4</td>
</tr>
<tr>
<td>Etoposide phosphate</td>
<td>0.09</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>4, 6</td>
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<tr>
<td>Fludarabine</td>
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<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>IMG</td>
<td>5</td>
</tr>
<tr>
<td>Foscarnet Sodium</td>
<td>13.00</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>5</td>
</tr>
<tr>
<td>Ganciclovir Sodium</td>
<td>0.35</td>
<td>IMG</td>
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<td>IMG</td>
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<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
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<tr>
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<td>Propofol*</td>
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<td>NAA</td>
<td>4</td>
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<tr>
<td>Sodium folinate</td>
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<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
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</tr>
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<td>IMG</td>
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<tr>
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<td>IMG</td>
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<td>Vinorelbine</td>
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<td>NAA</td>
<td>NAA</td>
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</tr>
</tbody>
</table>

NAA = No Antimicrobial Activity
IMG = Inhibits Microbe Growth
*Also showed NAA to E. faecalis

All references listed at the end of presentation
# Microbiological Growth

## Table 2: Nutritional Solution Microbe Viability

<table>
<thead>
<tr>
<th></th>
<th></th>
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<td>Normal Saline</td>
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<td>NAA</td>
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<td>4,7, 14</td>
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<td>5% Dextrose</td>
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<td>NAA**</td>
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<tr>
<td>Lactated Ringers</td>
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<tr>
<td>Amino Acid Solution*</td>
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<td>NAA**</td>
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<tr>
<td>Casein Hydrolysate (in dextrose)++</td>
<td>NAA</td>
<td>IMG</td>
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<td>NAA**</td>
<td>NAA**</td>
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<td>9</td>
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<tr>
<td>Synthetic Amino Acids (in dextrose)++</td>
<td>IMG</td>
<td>IMG</td>
<td>NAA**</td>
<td>NAA</td>
<td>NAA**</td>
<td>NAA**</td>
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<td>NAA</td>
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<tr>
<td>10% Safflower oil</td>
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<td>NAA</td>
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<td>10% soybean oil</td>
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<td>10</td>
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<tr>
<td>10% fat emulsion (Travumulsion 19%)</td>
<td>NAA</td>
<td>IMG</td>
<td>NAA**</td>
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<td>NAA**</td>
<td>NAA**</td>
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<tr>
<td>20% fat emulsion (Travumulsion 20%)</td>
<td>IMG</td>
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<td>NAA**</td>
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<tr>
<td>40% lipid TNA #</td>
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<td>NAA</td>
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<td>NAA</td>
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<td>NAA</td>
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<tr>
<td>25% lipid TNA #</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
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<td>NAA</td>
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<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>11</td>
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<tr>
<td>Albumin 6.25 g (in 0.9% sodium chloride)</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>12</td>
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<tr>
<td>TPN (containing Albumin)</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>NAA</td>
<td>IMG</td>
<td>NAA</td>
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<td>12</td>
</tr>
</tbody>
</table>

* Aminofusion®, IMG to B. fragilis
** C. albicans was able to proliferate to almost double its colony size in these solutions.
 (+) Hypotigen®
 (+++) Freamine®

# Percent based on caloric content

NAA = No Antimicrobial Activity
IMG = Inhibits Microbe Growth
CDC Update on Alabama PN Case

• Sterile filters used to sterilize CSPs shall be:

  – Pyrogen-free and have a nominal porosity of 0.2 um or 0.22 um.

  – Certified by the manufacturer to retain at least 107 microorganisms of a strain of Brevundimonas (pseudomonas) diminuta per cm² of filter surface area.

  – The filter dimensions and liquid material to be sterile-filtered shall permit the sterilization process to be completed rapidly, without the replacement of the filter during the process.
CDC Update on Alabama PN case

- CDC repeated the process using non-sterile API and made a batch of amino acid (AA) solution
- Inoculated the AA solution with the *Serratia marcescens*
- Used a 0.22 micron sterilizing grade filter
- Serratia got through both a 0.22 micron and 0.1 micron filter
- The filters passed its bubble-point

Don’t let the *Serratia* into your sterile compounding area!
Critical Factors in Aseptic Technique

Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. Trissel et al. 1

Objective: To determine if simple work practice changes could effectively reduce the potential contamination occurrence

Results:

<table>
<thead>
<tr>
<th>Group</th>
<th>Contamination</th>
<th>Type of Gloves</th>
<th>70% Isopropyl Alcohol (IPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>Non-sterile</td>
</tr>
<tr>
<td>A (Years 1 and 2)</td>
<td>28/539 (5.2%)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>B (Year 3)</td>
<td>3/311 (0.96%)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>C (Year 4)</td>
<td>1/296 (0.34%)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- Significant reduction in contamination:
  - Groups B + C compared to Group A (p=0.000018)
  - Group B compared to Group A (p=0.0029)
  - Group C compared to Group A (p=0.0005)

- Non-significant reduction in contamination:
  - Group C compared to Group B (p=0.3367)

Conclusions: The use of protective chemotherapy gloves that were repeatedly disinfected with IPA decreased the contamination rate of pharmacy-compounded sterile preparations


# Critical Factors in Aseptic Technique

**Table 1. Data Results**

<table>
<thead>
<tr>
<th>Agar Fingertip Testing</th>
<th>Bacterial Growth</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hand</td>
<td>13</td>
<td>63</td>
</tr>
<tr>
<td>Right (n = 76)</td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>Left (n = 78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Compounding (n = 77)</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>After Compounding (n = 77)</td>
<td>11</td>
<td>66</td>
</tr>
<tr>
<td>Type of Glove</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile (n = 80)</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Non-Sterile (n = 104)</td>
<td>25</td>
<td>79</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Mini-bag Testing</th>
<th>Bacterial Growth</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Time of Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Compounding (n = 39)</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>After Compounding (n = 40)</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>Type of Glove</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile (n = 38)</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Non-Sterile (n = 45)</td>
<td>2</td>
<td>43</td>
</tr>
</tbody>
</table>

- No significant difference in bacterial growth for the use of sterile versus non-sterile gloves in TSB mini-bags (p=0.855)
- No significant difference in contamination risk based on if the test was completed with new gloves or gloves used for at least 1 hour of compounding in TSB mini-bags (p=0.293) or TSA plates (p=0.21)
- Significant difference between bacterial growth and type of glove used in TSA plates (p<0.001); Odds ratio of 1.3 times more likely to have bacterial growth with use of non-sterile versus sterile gloves
- No significant difference in contamination risk based on which hand was used during compounding (p=0.732)

Critical Factors in Aseptic Technique

• "Alcohols used for skin disinfection prior to invasive procedures should generally be free of spores to avoid any contamination. Although the risk of infection is minimal, the low additional cost for a spore-free product is justified."

• **Illnesses in Children's Hospital Prompts Discovery of Contaminated Alcohol Pads**
  – ScienceDaily (June 12, 2012) — A small cluster of unusual illnesses at a Colorado children's hospital prompted an investigation that swiftly identified alcohol prep pads contaminated with *Bacillus cereus* bacteria, according to a report in the July issue of *Infection Control and Hospital Epidemiology*, the journal of the Society for Healthcare Epidemiology of America. The investigation ultimately led to an international recall of the contaminated products.

• **Results:**

  – 10 operators previously trained in aseptic technique were assessed.
  – Overall operator failure rate was 40%
  – 2.3% of the 300 preparations were contaminated
  – 10 of 60 finger dabs were found to be contaminated with *E. faecalis*, the challenge microorganism.
  – NO association between operators’ years of experience and media-fill test results.

Direct Compounding Area (DCA)

The DCA is only the portion of the PEC where the Critical Site is exposed to unidirectional HEPA-filtered air during an aseptic manipulation.
Principles of “First Air”

• Good aseptic technique in sterile compounding requires the understanding and proper use of “First-Air”.
  
  – “First-Air” is the air exiting the HEPA filter in a unidirectional air-stream and is virtually free of particulate contaminants.
  
  – All critical manipulations must be carried out in the unobstructed “first air” zone in the direct path of the HEPA filter discharge.
  
  – Proper product and process placement with respect to the supply and discharge will provide a contamination free compounding area.
SDV checklist

• Disinfect the vial prior to use

• Vigorously wipe the vial septum in one direction using a sterile disinfectant agent and low-lint wipe.

• Allow vial septum to dry prior to penetrating it with a needle or spike

• Personnel must use aseptic technique and be properly garbed

• Use sterile gloves and perform routine glove disinfection with sterile IPA

• Keep the DCA clear of items and work in first-air
Pharmacy Bulk Package (PBP)

- USP <1> Injections
- Sterile preparation for parenteral use that contains many single doses
- Restricted to the preparation of admixtures for infusion or filling empty sterile syringes
- Closure penetrated only once
- Used in a suitable work area such as a laminar flow hood
- Includes a statement limiting the time frame in which the container may be used once it has been entered
Cefazolin 10 gram PBP

- Typical package insert
  - After entry, use entire contents of the vial promptly
  - Dispense within 4 hours of initial entry
  - Discard PBP vial within 4 hours after initial entry
FDA and Package Insert Information

- FDA NDMS Review of Label—must be approved by FDA—“A claim” - how will the product prepared at clinic prior to patient administration?

- Assessment of the information provided to the pharmacist and clinician regarding product preparation.
  - e.g.: how many preparation and dilution steps prior to final product for administration to patient?

- Assessment of the storage conditions of final product post preparation.
  - What are the storage temperature(s)?
  - What are the storage times?
  - What are the diluents?

- Does the application contain data to support the storage conditions?
FDA NDMS

• Sterile Products-Container Closure (C/C) Penetration
  – Significant factor that dictates the sterile integrity of the product in the container

• Assumption!
  – During penetration of the container closure system, microbes may have been introduced into the drug product.

• What is the microbiological product quality following C/C penetration?
  – Drug product immediately administered vs. drug product prepared and held for a period of time prior to administration

• Post Manufacturing Drug Product Preparation Prior to Patient Administration
  – Solids that are constituted with a diluent
  – Liquid admixtures
Reading Recommendation: Metcalfe, JW, Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration. American Pharmaceutical Review, Feb 1, 2009
• A product with a pharmacy bulk package-approved, post-penetration holding time of 4 hours was subsequently approved for an extended holding time of 10 hours after submission of data in a supplemental application demonstrating that the product does not support microbial growth.

• Challenge microorganisms (S. aureus, P. aeruginosa, E. coli, C. albicans, and A. niger) satisfied the USP 51 definition of no increase in growth when inoculated in the product and held at the intended storage conditions over the proposed extended holding period. The submission of this study led to approval of the extended post-penetration holding period of 10 hours.

# USP <797> Risk Levels

<table>
<thead>
<tr>
<th>Ingredient: CSP Relationship</th>
<th>Risk Level</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One to One (1:1)</strong></td>
<td>Low-Risk Compounding</td>
<td>• Reconstitution and transfer of a 1 gram vial of cefazolin into one syringe or minibag</td>
</tr>
<tr>
<td><strong>One to Many or Many to One (1:∞) or (∞ to 1)</strong> # components &gt; 3</td>
<td>Medium-Risk Compounding</td>
<td>• A bulk 10 gram vial of vancomycin distributed among several final doses • The combination of several ingredients (&gt;3) into one final dose (TPN)</td>
</tr>
<tr>
<td><strong>Any ingredient-CSP relationship using nonsterile ingredients and/or devices or a CSP that requires terminal sterilization (filtration, steam, heat, gas or ionizing radiation)</strong></td>
<td>High-Risk Compounding</td>
<td>• Alum bladder irrigation • PCA or epidural from powdered ingredients</td>
</tr>
</tbody>
</table>

Our responsibility

• To care for the patient, we must properly handle limited and life-saving medication through compliance with USP 797.

• Aseptic Technique is key

• Proper vial and vial septa disinfection practices with a sterile disinfectant is critical in preventing contamination from entering the SDV during the initial use and should be routinely repeated

• The use of sterile gloves and a sterile disinfecting agent is required to comply with the chapter
  — “Substantial” compliance with these requirements is not acceptable

• Maintain the vial in the ISO Class 5 PEC at all times

• Discard vial after 6 hours or according to the manufacturer’s package insert

• Treat all CSPs repackaged from SDVs as a medium-risk level CSP
“You can avoid reality, but you cannot avoid the consequences of avoiding reality.”

Ayn Rand (1905-1982)
References


Thank you

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