Institute for Safe Medication Practices Sterile Preparation Compounding Safety Summit

**DRAFT OF THE PROCEEDINGS**

**Introduction and Background on Sterile Preparation Compounding Safety**

The Institute for Safe Medication Practices (ISMP) held a national invitational Sterile Preparation Compounding Safety Summit on October 25-26, 2011 at the ACE Conference Center in Lafayette Hill, PA to address frequent and numerous reports of critical intravenous (IV) compounding errors. Such errors were identified via the ISMP's National Medication Error Reporting Program (ISMP-MERP), other reporting programs (e.g., U.S. Food and Drug Administration's MedWatch and MEDMARX), scientific literature, and the lay press. Many of these reports highlighted fatal medication errors, often involving infants or children, associated with mistakes made during IV compounding in pharmacies. Clearly national efforts are needed to identify and eliminate or reduce causative factors.

The summit focused on establishing, by consensus of over 60 invited attendees, guidelines, safe practices, and standard operating procedures (SOPs) needed to ensure the safe preparation of compounded sterile preparations (CSPs), especially IV admixtures. The summit comprehensively reviewed current methods used to prepare CSPs, identified manual and automated safeguards that help provide assurance that the proper preparation is dispensed for administration, addressed barriers that could inhibit safe practices, and sought to identify and standardize critical quality control practices needed for preparing and verifying the quality and safety of the final CSP.

Attendees were surveyed prior to the summit to gather information about their facilities, preparations compounded, standard practices, quality controls, automated processes, and software used related to CSPs. Participants were asked to review and comment on a compendium of ISMP recommended best practices that was sent to all attendees prior to the summit. Those practices with less than 90% agreement by attendees were included for discussion during the summit.

Summit participants came from a variety of backgrounds including pharmacy technicians, staff pharmacists, nurses, medication safety officers, and pharmacy leaders from hospitals of various sizes as well as representatives from the health care industry, patient safety organizations, the U.S. Food and Drug Administration (FDA), the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), and the American Society of Health-System Pharmacists (ASHP).

Based on the pre-summit survey, one-third of responding participants
represented hospitals with 100-299 beds and half were from hospitals with over 500 beds.

The goals for the summit included:

1) Review of currently employed quality control measures used to ensure the correct preparation of CSPs.
2) Identification of quality control practices that should be standardized for incorporation into the manual process to ensure the correct preparation of CSPs.
3) Description of current and emerging technologies that assist the preparation of CSPs and how these technologies are utilized.
4) Identify the minimum safeguards that must be in place to prepare and dispense CSPs.
5) Recommend best practice guidelines to ensure the safe preparation of CSPs by pharmacies in acute care facilities.

At the summit, participants were asked a variety of questions regarding best practices when applied to preparation of 1) simple CSPs (those with one or two ingredients, such as patient controlled analgesia infusions, single electrolyte infusions, bolus doses, or maintenance IV infusions with no more than two ingredients), 2) complex CSPs (those with greater than two ingredients, such as parenteral nutrition (PN), cardioplegia solutions, or dialysis solutions), 3) pediatric and neonatal preparations, and 4) chemotherapy.

The remainder of this report will discuss agreed upon consensus statements for CSPs. Most of the consensus statements fit with a particular core process, but some span several core processes. Consensus statements are provided for the following core processes in the following order:

- Policies and Procedures for Compounding Sterile Preparations
- Order Entry and Verification
- Drug Storage
- Assembling Products and Supplies for Preparation
- Compounding
- Drug Conservation
- Preparation of Source/Bulk Containers
- Technology/Automation Used for Compounding CSPs
- IV Workflow Software
- Automated IV Compounding Devices
- Quality Control/Final Verification of Manually Prepared Product
- Product Labeling
- Record Keeping
- Staff Management

Note: words that are in all capital letters have a definition in the glossary section at the end of the document.
Policies and Procedures for Compounding Sterile Preparations

- Organizational practices SHALL comply with USP <797> standards.
- Organizations MUST have well-defined policies and procedures that guide the compounding of sterile preparations.
- Organizations must identify standardized work flow processes that include quality control, process change control and documentation practices. It is recognized that work flow may vary depending on the type and quantity of CSPs prepared and the sophistication of technology employed in each organization.
- Organizations SHOULD develop a drug conservation policy that addresses the handling and disposition of drugs (while maintaining their integrity and sterility) that may be in short supply due to market conditions, as these shortages can affect work flow conditions.
- Organizations shall develop detailed policies for BATCH production of CSPs. Batch processing policies for simple, complex, pediatric, and chemotherapeutic CSPs should include detailed preparation instructions and references when available.
  - Batch processing formulas shall be provided for all batch sizes (e.g., production of a 50 mL batch vs. a 250 mL batch), document theoretical yield versus actual yield, and account for all waste.

Order Entry and Verification

- All orders entered into a computerized prescriber order entry (CPOE) system must be verified by a pharmacist. All orders entered into a pharmacy information system or transcribed onto pharmacy patient profiles by a non-pharmacist must be verified by a pharmacist in accordance with state rules and regulations.
- For orders requiring pharmacy transcription, the information entered into the pharmacy system or transcribed onto pharmacy patient profiles shall be verified by a second QUALIFIED individual, even when the order was entered by a pharmacist, for specific types of CSPs and/or selected individual products as identified by the organization (e.g., chemotherapy, PN, other selected high-alert medications).
  - This review shall include a comparison of the order to the pharmacy generated label. Such a transcription review should be performed
for chemotherapy, complex CSPs, pediatric/neonatal CSPs and other CSPs as defined by the organization.

- For PN, the sequence of ingredients on any pre-printed order sets or order entry screens should be consistent with that of the automated IV compounding screens, the patient-specific label and the medication administration record.

**Drug Storage in Sterile Compounding Areas**

- Minimize drug inventory to avoid intermingling of products.
- Provide sufficient space for drug storage to segregate each drug concentration.
- Concentrated electrolytes shall be isolated from other inventory.
- Labeling of bins or bin dividers should include generic drug name, and concentration.
- FDA and/or ISMP tall man lettering should be employed for look-alike and sound-alike drugs.
- CSPs that have been compounded, and are waiting to be checked shall be placed in a clearly identified and designated storage location until the checking process has been completed.
- Environmental recommendations, as provided in the USP <1066>, for lighting, noise, workspace and distractions should be followed.

**Assembling Products and Supplies for Preparation**

- Drugs, diluents, base solutions and other supplies should be gathered and placed in a separate container, (e.g., a basket or bin) for each preparation or each batch to be prepared. When possible, person gathering products should be different than the person preparing the CSPs.

**Compounding**

- When available, commercially-prepared, premixed IV products should be used over manually compounded sterile products.
Additives should not be manually incorporated into a commercially-prepared, pre-mixed solution other than those designed for the addition of additives, e.g., dual chambered bags for parenteral nutrition.

Standard base solutions (e.g., dextrose 5%) shall be used when available to prevent the error prone process of preparing unique/unusual base solutions (e.g., dextrose 3.5%).

Outsourcing the production of CSPs should be considered as an alternative to in-house compounding when:

- the volume of certain CSPs is very low, thus making it difficult to maintain staff competency for preparing the product.
- the volume for certain CSPs is high and staff resources are limited or unavailable to prepare this quantity.
- the organization does not possess the technological resources to prepare certain products according to USP <797>.
- commercially-prepared, premixed product is not available, e.g., product shortages.

Organizations should use a tool, such as the ASHP Foundation’s document, “Outsourcing Sterile Products Preparation: Contractor Assessment Tool” (http://www.ashpfoundation.org/sterileproductstool), as one resource to analyze the capabilities and quality of external compounding providers prior to selecting a vendor.

Standard operating procedures for compounding all CSPs shall be established and sufficiently detailed to prevent process variation in practice among practitioners.

Formulas (ingredients and the process to prepare) shall be established and standardized by the organization and used to guide the compounding of complex CSPs, (e.g., dialysis solutions, cardioplegia solutions, dilutions, aliquots).

- SOPs and formulas should be supported by current literature and periodically revised as new information becomes available.
- Pharmacy staff members compounding CSPs shall follow the sequence of steps and processes specified in the formulas and SOPs.
A preparation label, master formulation record, or worksheet should be available for compounding chemotherapy, complex, and pediatric/neonatal CSPs. This document should express drug name, base solution, patient-specific dose, preparation calculations, final volume of the preparation and identify the appropriate drug dosage form to be used (e.g., concentration and size of the container).

Only one staff member is permitted to work in the DIRECT COMPOUNDING AREA when compounding chemotherapy and complex CSPs.

Two staff members are permitted to work in the compounding area simultaneously, if necessary, provided that the hood is 6 feet in length and a physical divide can be maintained between staff members, and the products being compounded are non-chemotherapy CSPs.

Only one CSP should be prepared at a time. An exception is:

- One practitioner can prepare multiple CSPs safely in the hood at one time only if preparing the same doses of the same drug with the same route of administration for one or multiple patients. It is not safe to prepare multiple CSPs at the same time in the hood for different doses or routes of administration, or multiple products for the same patient.

In facilities that care for adult, pediatric and neonatal patients, the computerized label runs for pediatric and neonatal CSPs shall be generated or printed separately from adult CSPs.

In facilities that care for adult, pediatric and neonatal patients, the preparation of CSPs for each population shall be separated by time or location. Separation strategies can include the use of different color bins for assembling products to be prepared.

Preparation of chemotherapy and complex CSPs shall only be performed based on the availability of qualified staff resources.

- Prescribers should comply with predetermined cut-off times that have been established by the organization to permit safe preparation of CSPs.

Pharmacies shall create standard processes to address the volume of base solution when compounding CSPs. Such standard work practices address:
if and when there is a need to remove base solution in amounts equivalent to drug additive(s).

if and when there is a need to eliminate the manufacturer overfill from the base solution and the method used to accomplish removal (e.g., direct removal of overfill volume or pumping the amount of base solution from a commercial container into an empty bag).

Drug Conservation

- Partially used multidose vials, bulk containers or single dose containers should not be left in the hood or direct compounding area for future use.

  - However, drugs in short supply that are covered by an organization-specific, drug conservation policy may be left in the hood. The conservation policy must include safe practices that address:

    ✓ Maintaining the integrity and sterility of these medications.
    ✓ Methods used to segregate the drug from the direct compounding area. Partially used vials of insulin, heparin, concentrated electrolytes or neuromuscular blocking agents shall never be left in the hood.
    ✓ Heparin and insulin vials shall never be in the hood at the same time.
    ✓ A pharmacist must perform a regular assessment of drug products stored in the hood for compliance with this policy.

Preparation of Source/Bulk Containers

- A detailed standard process shall be in place for preparing and checking pharmacy-compounded SOURCE/BULK CONTAINERS used to prepare multiple doses or batches.

  - A pharmacist shall INDEPENDENTLY DOUBLE CHECK all diluents and drugs before the preparation of all source/bulk containers.

  - Source/bulk containers prepared for use during compounding shall be labeled with the following information:

    ✓ drug name
    ✓ concentration
    ✓ diluent
Technology/Automation Used for Compounding CSPs

- Organizations should develop a strategic plan for implementation of automation and technology for the sterile products service.
- Technology and automation such as bar code verification or IV robotics should be utilized as much as possible for preparing and verifying CSPs.
- Routine preventive maintenance must be performed, and calibration and certification shall be current and documented, for equipment used during the compounding of CSPs.
- All current service releases for software in use should be installed and tested.

IV Workflow Software

- Intravenous workflow software (e.g., DoseEdge, Script Pro Telepharmacy, and I.V. Soft or similar technology) should be used to augment manual processes whenever possible.
- IV workflow software shall be well-maintained, and appropriately programmed with adequate infrastructure to support the system.
- Organizations shall have SOPs that ensure that the final check of the preparation has been completed prior to dispensing.

Automated IV Compounding Devices

- Privileges to make changes in the database shall be restricted to a limited number of staff who are well-trained in both the theory and the mechanics of this process.
- The use of a checklist/sign-off sheet shall be required when adding new products, new generics, and changes in vial size or when making other modifications to the database (e.g., changes in privileges, changes in data
requirements). Two staff members shall be required to sign off or validate changes. (This process would not apply to inputting a new lot number for a product already in the database.)

- Organizations shall implement specific soft limits and hard (catastrophic) limits for ingredients that are consistent with the needs of their patient population.

- Weight-based warning limits for doses should be developed by vendors. As an alternative, hospitals may develop and use their own weight-based warning limits.

- Only pharmacists shall be allowed to override alerts.

- Bar code verification shall be used to verify product identity during set up and replacement of ingredients.

- A double check process for the initial daily set up shall be performed, with two staff members using a printed check list. Verbal affirmation should take place to validate placement of all additives and base solutions including name, concentration, and container size.

- Tubing set(s) shall be traced from the source container to the port where it is attached during the initial daily set up and with each change in the source container.

- If multiple containers of a single additive are used during the preparation of a single CSP, all empty containers shall be presented to the pharmacist as part of the final check process prior to dispensing the final CSP.

- Staff must be trained in the use of this technology, and there is documentation of initial training, as well as ongoing competency assessment.

- The label generated by the IV compounding device should ideally be the only label attached to the completed CSP. Ensure this label reflects the sequence of ingredients and units of measure as presented on the prescriber’s original order.

- Customized order entry templates created by organizations should have a documented standard review process by qualified staff, that includes review and testing of the clinical decision support that is expected to alert the pharmacist to significant warnings. The use of a checklist/sign-off sheet shall be required and two staff members, (including at least one pharmacist) shall sign off or validate the template.
When an automated IV compounder is used, it should deliver all ingredients. Manual compounding should only be used:

- if the volume of an ingredient to be mixed is less than the compounder can accurately deliver.
- if there is an interaction between an ingredient and a component of the compounder (e.g., insulin and tubing).
- if there is a chemical interaction between ingredients that cannot be mitigated by sequencing the addition of ingredients.

**Quality Control/Final Verification of Manually Prepared Product**

- All personnel shall be able to “stop the line” and question any concerns about any order or any sterile preparation to be compounded.
- A visual check shall be performed to verify the accuracy of all diluents and drugs (including volumes and concentrations).
- Organizations that do not use IV workflow software shall identify in their compounding policies those CSPs that require preproduction visual confirmation of the amount of each ingredient (**prior to** addition to the final container). At a minimum this list should include the following:
  - chemotherapy
  - PN admixtures
  - pediatric and neonatal preparations
  - pharmacy prepared source/bulk containers
  - preparations requiring the use of multidose vials of high-alert medications (e.g., insulin, concentrated electrolytes, heparin)
  - CSPs administered via high-risk routes of administration (e.g., intrathecal, epidural, and intraocular)

Proxy methods of verification such as the SYRINGE PULL-BACK method of verification shall never be used in the preparation of chemotherapeutic, complex, pediatric/neonatal or high-alert CSPs and shall not be used without the presence of the actual, original source containers (medication and diluent). Handwriting the amount of an additive on the final product label shall not be used as the sole method of verification of any CSP.

- Errors that occur during the compounding of CSPs, and are identified by either the pharmacist or technician prior to dispensing, should be documented and reported through the organization’s reporting system for analysis.
Serious incidents should be reported to the ISMP Medication Error Reporting Program (ISMP forwards reports to FDA MedWatch) for learning purposes and dissemination of prevention measures.

The use of proactive risk assessments, such as failure modes and effects analysis (FMEA) are recommended prior to the implementation of process changes.

Internal as well as external information about medication errors, from sources such as ISMP, should be reviewed and used to modify practices and procedures as needed.

Product Labeling

ISMP label guidelines should be utilized when formatting computer generated labels for CSPs. These are available at http://www.ismp.org/Tools/guidelines/labelFormats/Piggyback.asp.

Labels shall be applied immediately *after* manual preparation of CSPs. (When certain technology is employed it may be necessary to apply the final product label prior to compounding the solution.)

Labels generated by an automated IV compounding device should match the format and units of measure of the prescriber’s order, include the beyond use date, and should ideally be the only label attached to the completed CSP. Preparation labels (or “prep tickets”) should never be used as the final product label.

For chemotherapy and other CSPs identified by the organization, the final volume (e.g., bag volume + manufacturer’s overfill + additive volume) to be infused shall be present on the label.

Information on the final label should match the format and units of measure of the prescriber’s order and the medication administration record. The product label should not contain unnecessary information (e.g., vial size used to prepare the CSP).

Record Keeping

When preparing CSPs intended for storage for anticipated needs, batch records should include:

- Date of production
Staff Management

- Pharmacy technicians involved in preparation of CSPs should be Certified Pharmacy Technicians having passed the appropriate tests administered by the Pharmacy Technician Certification Board.
- All staff members involved in preparing CSPs or supervising the preparation of CSPs shall participate in a comprehensive orientation and training program as well as an ongoing competency assessment program.
- Pharmacists and pharmacy technicians who prepare CSPs should have annual competency evaluation for all aspects of sterile compounding which might include:
  - performing calculations and preparing dilutions
  - compounding base solutions
  - using aliquots as a method of measuring ingredients below the sensitivity of a scale (by proportional dilution with inactive ingredients)
  - aseptic technique including media-fill testing
  - preparing medications for complex routes of administration (e.g., intrathecal)
  - proper use of technology (if available)
- A national certification program for sterile-compounding specialists should be developed.
- The American Association of Colleges of Pharmacy should instruct their Academic Affairs Committee to add hands-on experience with sterile compounding into pharmacy training to achieve minimum competencies, which should be developed by an interdisciplinary stakeholder group.
Acknowledgements

The Institute for Safe Medication Practices would like to thank all of the participants at the ISMP Sterile Preparation Compounding Safety Summit for volunteering their time and expertise in developing the content of these guidelines. See Appendix A for a list of summit participants.

Glossary and Abbreviations

- **Batch** – Preparing a number of non-patient specific doses with the intention to use based on future patient need.
- **CSP** - compounded sterile preparation
- **Direct compounding area** – the area within the hood where the critical site (vial septum and needle) are exposed to first-air.
- **Independent double check** - a procedure in which two individuals, preferably two licensed practitioners, separately check each component of the work process.
  An example would be one person calculates a medication dose for a specific patient and a second individual independently performs the same calculation (not just verifying the calculation) and then matching their results.
- **Must** - used to indicate a requirement established by law, regulation, accreditating bodies, or other binding authorities.
- **PN** – parenteral nutrition
- **Qualified individual/staff** – staff members adequately trained and approved to perform a particular function.
- **Shall** - used to indicate a minimum standard of practice set forth in this document.
- **Should** - used to indicate a best practice that is strongly encouraged but which may not be applicable to all institutions or in all circumstances.
- **SOP** – standard operating procedure
- **Source/bulk container** – a sterile container (bottle, vial, or bag) manufactured by a commercial vendor or prepared by pharmacy, which is then used as a source from which to withdraw multiple doses.
Syringe pull-back – presentation of the syringe(s) pulled back to display amount of medication or diluent that was added to the infusion container AND the actual drug or diluent source container(s) from which the drug or diluent was withdrawn prior to the addition to the infusion container.

Additional Topics

The following topics were briefly discussed at the summit but there was no consensus for a recommendation. These would require additional discussion before a recommendation can be made. Please provide your thoughts on:

1) Manufacturer overfill in IV solution containers

2) End product testing technology (verification of accurate compounding)

The topic of record keeping was discussed at the summit and these were the recommendations developed. This topic needs additional review and comments and we would appreciate your comments on the information below.

Record keeping

For CSPs defined by the organization, permanent documentation (ideally electronic) should be readily available and retained in accordance with state regulations. These records should be available in the event of a drug recall to identify patients who have received the drug, or during an investigation of safety issues involving potentially substandard or adulterated drugs. Permanent documentation should include:

- National Drug Code number(s) of ingredients
- Lot number(s) of ingredients
- Expiration date(s) of ingredients
- Beyond use date for the preparation
- Person preparing the CSP
- Person verifying the CSP
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