Conserving Drugs with Sterile Compounding during the COVID-19 Pandemic

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Conserving drugs with sterile compounding during the COVID-19 pandemic

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Disclosures

• I have no conflicts of interest to declare
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Learning objectives

1. Understand 4 broad sterile compounding approaches that help conserve supply of non-hazardous sterile medications
2. Apply these strategies to current or potential drug shortages with real-life case examples
3. Appreciate considerations for staffing in the cleanroom, PPE use, medication safety, patient outcomes and stakeholder engagement
4. Familiarize with evidence-based resources that support compounding initiatives
Why conserve medications?

- Distributors such as McKesson are enforcing purchasing allocations
- Sites likely ordering more drugs than usual to prepare for influx of patients
- Higher uses of certain drugs due to the nature of COVID-19 infections and their complications
- Higher patient volumes
- Overlap of drug utilization across different areas of care - e.g., palliative and critical care
- All of the above worsen existing unresolved drug shortages
How can sterile compounding help?

1) Repackaging

- **Simplest to implement**
- **Aliquoting**: direct transfer of drug from original container to smaller ones
- **Pooling**: combining drugs from several containers into a larger container
- **Stability** implications: Is the drug stable in the new **container** and for **how long**?
- **Stability** implications: Is the drug stable with the **compounding equipment**? (i.e., pump tubing)
- **Sterility** implications: Generally Medium Risk with any batching activity is assigned **Beyond-Use Dates (BUD)** of 9 days refrigerated and 30 hours room temperature **in a NAPRA-compliant facility**
  - Final assigned BUDs must be the shorter date of the stability and sterility BUDs
- **Example of when aliquoting is useful**: When only small quantities of each container are needed per dose
Case examples relevant to COVID-19

Aliquoting example: Hydromorphone 10 mg/mL 1 mL vials

- Projected shortage due to anticipated higher use of palliative services
- Most breakthrough or starting doses are 0.5-1 mg
- Flip top vials vs. glass ampoules
  - Aliquot into 1 mg/0.1 mL batches
  - Stability with new container? Stable in polypropylene (most syringes), polycarbonate
  - Sterility? Generally 9 days fridge/30 hours room
Case examples relevant to COVID-19

Pooling example: Propofol 10 mg/mL in lipid emulsion

- Projected shortage of 100 mL bottles (ICU) and accumulation of 20 mL vials (OR)
- Are 50 mL bottles commercially available and orderable?
- Pool 20 mL vials of propofol into an infusion bag
  - **Stability** with material of the bag? Adsorbs onto PVC, leaches DEHP, but considerably more compatible with polyolefins (polypropylene, polyethylene, propylene-ethylene copolymers)
  - **Stability** with pump tubing for pooling? Tubing is PVC but DEHP-free. Flowing propofol exhibits less PVC adsorption than stagnant propofol
  - **Sterility**? Generally 9 days fridge/30 hours room BUT: lipid emulsion is a great growth medium for microorganisms
    - Infusion time recommendations for 3-in-1 TPN vs. piggybacked lipids vs. propofol in lipid emulsion
    - What is a stronger driver of sterility - presence of a preservative or strict adherence to sterile technique?
    - 12 hour infusion time for 0.005% EDTA-containing formulations; conflicting recommendations for preservative-free forms
Tubing for compounding pump
How can sterile compounding help?

2) Dilution

- Dilute an original product to produce quantities of a desired concentration
- Repackage the diluted product in a sterile container
- Stability implications: Is the drug stable in the diluent at the new concentration in the new container and for how long?
- Sterility implications: Generally Medium Risk with any batching activity is assigned BUDs of 9 days refrigerated and 30 hours room temperature in a NAPRA-compliant facility
- Example of when this is useful: Shortage of a drug at a desired lower concentration
How can sterile compounding help?

3) Formulate a new CSP (compounded sterile product) from a manufactured product if not commercially available/orderable

- Investigate concentrations and volume sizes desired in clinical practice
- **Stability** implications: Is the drug stable in the *diluent* at the new *concentration* in the new *container*?
- **Sterility** implications: Generally Medium Risk with any batching activity is assigned BUDs of 9 days refrigerated and 30 hours room temperature *in a NAPRA-compliant facility*
- **Example of when this is helpful**: To serve as an alternate option to first line therapy that is in shortage, or conserve the drug in shortage for other more pertinent indications
Case examples relevant to COVID-19

New formulation example: Hydromorphone 0.2 mg/mL bag for continuous infusion

- Projected shortage of fentanyl vials for compounding of fentanyl drips in the ICU
- Investigate other opioids of choice, desired concentrations and infusion rates used in critical care
- **Stability** in diluent and container? Stable in NS and with PVC (material in most bag types)
  - Consider manufacturer-specified target fill volumes and overfill ranges of diluent bags
  - Decide which of the three ISMP Canada compounding approaches to use to account for overfill
- **Sterility**? Generally 9 days fridge/30 hours room
Case examples relevant to COVID-19

New formulation example: Propofol in MAID kits

- Previously at PRHC, each kit consisted of 2 grams propofol compounded into pre-filled polypropylene syringes from 2 x 10 mg/mL 100 mL bottles
- Now compounded from 10 x 10 mg/mL 20 mL vials instead to conserve 100 mL bottles for ICU infusions
- 2 days later CIVA receives a MAID request
- Stability (polypropylene unchanged) and sterility (BUD 6 hours) unaffected
How can sterile compounding help?

4) Compounding from non-sterile ingredients

• Raw API (active pharmaceutical ingredient) is not sterile
• Falls under NAPRA High Risk level compounding; not recommended unless facility has supports in place
• (Using non-sterile equipment in the cleanroom also constitutes as high risk compounding, i.e., a scale)
• Diluent of choice, stabilizers, preservatives, pH buffers, terminal sterilization, sterility and stability testing may be involved
How can sterile compounding help?

• Regardless of approach used, any kind of sterile compounding must be done by trained, competent and tested personnel in a NAPRA-compliant facility

• All primary and secondary engineering controls in place

• Quality assurance of personnel competence, i.e., gloved fingertip sampling (GFS) and media fill and environmental sampling (air and surface) in place

• Compounding worksheets are reviewed on a regular basis for compounding process and BUD validity
Other strategies

Maximize utility of point-of-use CSPs

• Example: Minibag Plus® docking systems - compatible with single-dose vials with powder or solution (up to 10 mL) with 20 mm vial closure
• Allows longer BUDs (up to 30 days before activation) and therefore potentially less drug wastage before BUD is reached

Explore outsourcing options

• Ontario: Drug Preparation Premises (DPP) - Baxter CIVA, Fresenius Kabi
• These establishments can also run into the same problems - shortage of ingredients, equipment and/or staffing
Considerations - high use patient care areas and ingredients

- Sedatives and analgesics of choice overlap in palliative care and critical care; both may also see higher patient volumes during COVID-19 pandemic
  - Fentanyl, hydromorphone, morphine, midazolam
  - Consider shortage of one drug impacting both service areas; what can intensivists and palliative care physicians do now to streamline treatment approaches?
  - Consider shortage of a single dosage form impacting different CSPs (e.g., fentanyl 50 mcg/mL 20 mL vials used to compound both continuous infusions for ICU and fentanyl CADD cassettes for pain pumps in palliative care)
Considerations - product safety and staff wellbeing

- **Implications of increased reliance on sterile compounding team:**
  - Mental and physical fatigue; compounding new and complex CSPs in a stressful environment increases risk of compounding error
  - Implement new CSPs sooner rather than later. Several benefits: early conservation, likely still have a supply of fresh PPEs to use each time, less stressful to implement new CSPs before the influx of patients occurs
  - CSPs involving opioids and other controlled substances may require IDC (independent double checks) in the compounding process
  - More compounding = more PPE use
  - May be more difficult to sustain new CSPs if a staffing crisis occurs, i.e., when compounders are infected with COVID-19 and are removed from the roster for 14 days at a time
    - Proactively plan for teams of compounders to not infect each other
    - Protect unique skill sets. ASHP and CSHP have forums discussing this
Considerations - PPE affects product safety

- **PPE conservation: (for sterile non-hazardous compounding, PPE protects the product from the compounder)**
  - Revisit staffing and workflow in the cleanroom - are there more people compounding at the same time than necessary?
  - Consider ‘soft’ cut-off times for CIVA to receive new orders for CSPs
  - Frequency of CIVA call-backs (wasting 2 sets of PPEs at a time)
  - Revisit CSPs that have traditionally required Independent Double Checks (IDC)
  - Look to other resources for PPE conservation/re-use (only if absolutely necessary) and implications on BUD
    - USP, Critical Point, FDA (recently released guidelines on PPE!)
    - Most important body parts to protect the product from: forearms, hands
    - Start gathering supplies early - sleeves to protect gowns, sterile gloves, surface sampling supplies, supplies to make your own sterile IPA if it goes on shortage
Considerations - stability affects patient safety

• The tested product on which stability data was published will not always exactly match the CSP that is desired in clinical practice
  • First, do no harm
  • Risk-based approach: balance risk of data extrapolation against risk of not providing a patient access to critical drug therapy enabled by compounding
  • Assess the mechanism of the instability if the product might be unstable:
    • Is it degradation? Is the degradant toxic to the patient?
    • Is it adsorption? Can the reduced drug concentrations be compensated by the titratable nature of the drug?
# Mechanisms of Instability

## Table 1. Common Factors Affecting Drug Stability

<table>
<thead>
<tr>
<th>Factor</th>
<th>Incompatibility or Instability</th>
<th>Common Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact with metal (e.g., needles or components of devices)</td>
<td>Chemical reaction</td>
<td>Hydralazine, metronidazole (with aluminum)</td>
</tr>
<tr>
<td>Freezing temperature</td>
<td>Inactivation, denaturation, emulsion cracking</td>
<td>Heparin, filgrastim, erythropoietin, lipid-containing TPN</td>
</tr>
<tr>
<td>Large organic anions and cations</td>
<td>Precipitation or formation of insoluble complex</td>
<td>Heparin with aminoglycosides</td>
</tr>
<tr>
<td>Light (natural and room)</td>
<td>Accelerated chemical degradation reactions</td>
<td>Dobutamine, furosemide, cisplatin, hydroxyzine, carboplatin</td>
</tr>
<tr>
<td>Low temperature (refrigerated)</td>
<td>Crystallization or precipitation</td>
<td>5-fluorouracil, furosemide, acyclovir, metronidazole</td>
</tr>
<tr>
<td>Plastic containers, sets, in-line filters</td>
<td>Adsorption of lipophilic agents—especially important at low concentrations</td>
<td>Sufentanil, filgrastim, calcitriol, midazolam, ainesulekin, insulin</td>
</tr>
<tr>
<td>PVC or flexible plastic container permeability</td>
<td>Evaporation, with resultant over-concentration of solution</td>
<td>PVC or flexible plastic containers distributed in overwrap bags; small volume bags are most susceptible</td>
</tr>
<tr>
<td>Plasticizer content of PVC containers, sets</td>
<td>Leaching carcinogenic plasticizer DEHP from DEHP-containing PVC</td>
<td>Paclitaxel, lipid emulsion, cyclosporine</td>
</tr>
<tr>
<td>Saturation solubility exceeded</td>
<td>Precipitation or crystallization</td>
<td>Morphine sulfate, etoposide</td>
</tr>
<tr>
<td>Temperature above 8°C</td>
<td>Accelerated chemical degradation reactions</td>
<td>Ampicillin, others</td>
</tr>
</tbody>
</table>
Considerations - sterility affects patient safety

- Conservative sterility BUDs can render compounding by CIVA less practical (i.e., BUDs shorter than 24 hours)
  - Risk-based approach: what are the sterility risks of nursing compounding on the floors vs. CIVA compounding?
  - What is the risk of extending the sterility BUD beyond usual recommendation?
    - Do a literature search - Health Canada, CDC, FDA, ISMP Canada/U.S., ASPEN (propofol)
    - How will you mitigate the risk?
    - How will you justify extension of the sterility BUD?
    - Consult your institution’s Risk Management Team?
  - Depending on your assessment of risk to the patient, manufacturer-specific sterility considerations will take precedence over sterility BUDs established by NAPRA/USP <797>
Considerations - engaging stakeholders

• Engage stakeholders early
  • Communicate early and clearly
  • Prescribers of high shortage risk drugs need to be aware and start thinking about their prescribing practices
  • Assess feasibility of compounding any new CSPs by consulting expertise from compounding, medication safety and systems, pharmacy informatics, purchasing, IV pumps, nursing and nurse educators, risk management
• Encourage innovation and open communication
Considerations - engaging stakeholders

• Engage stakeholders early
  • Turnaround times for responses to medical information requests from drug companies can take up to 2 weeks (or longer): **start gathering information early**
  • How long your drug supply lasts can largely depend on how early you implement proactive conservation measures
    • i.e., an unexpected surge of patients needing ICU care may wipe out your fentanyl supply due to a lack of pre-planned alternative, leaving none for CADD compounding for palliative patients
Select drug stability and sterility resources

- Trissels IV Compatibility and Trissels Drug Monographs (access through Lexicomp subscription)
- AHFS monographs (open access until May 15, 2020): www.ahfscdi.com (username: ahfs@ashp.org, password: covid-19)
- Stabilis® Database (free access): www.stabilis.org
- CSHP QIDs: COVID-19 (open access), Parenteral, Compounding, Drug Information
- ASHP Connect Communities: COVID-19 (open access)
- Drug information service subscriptions
- Drug and materials manufacturers: internal stability data, container sizes, container materials, fill targets, overfill volumes, additive capacity
- NAPRA sterile non-hazardous compounding standards: https://napra.ca/general-practice-resources/model-standards-pharmacy-compounding-non-hazardous-sterile-preparations
Select papers on the fundamentals of sterile packaging systems


Select propofol and lipid-specific resources


• Sacks GS and Driscoll DF. Does lipid hang time make a difference? Time is of the essence. *Nutrition in Clinical Practice* 2002;17:284-290

Compounding-specific PPE resources

• U.S. Pharmacopoeia (USP):

• Critical Point:

• U.S. Food and Drug Administration (FDA)
Thank you!

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