The Art & Science of: Compounding Ophthalmic Preparations

Michael J. Freudiger, PharmD, APh, BCPS, BCGP

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Disclosure Information

The Art & Science of Compounding Ophthalmic Preparations
Michael J. Freudiger, PharmD, APh, BCPS, BCGP

• I have no financial relationships to disclose.
AND
• I will not discuss off-label use and/or investigational use in my presentation.
At the completion of this activity, you will be able to:

• Review the anatomy of the eye to distinguish the requirements of compounded preparations for each unique site of administration.

• Demonstrate the process of developing master formulas for sterile ophthalmic preparations.

• Review the compounding staff's education and processes to increase patient safety.
Ophthalmic Preparations?
Tobramycin 14% fortified ophthalmic solution
Instill 1 drop every 1 hour x 3 days
Question: Would you proceed to fill this order?

Vancomycin 5% fortified ophthalmic solution
Instill 1 drop every 2 hours x 7 days
Ceftazidime 2.25 mg/0.1 mL intravitreal injection
Injected by physician during surgery
Question: Would you proceed to fill this order?

Voriconazole 50 mg/0.1 mL intravitreal injection
Injected by physician during surgery
Question: Would you proceed to fill this order?

Amphotericin B 5 mcg/0.1 mL intravitreal inj. Injected by physician during surgery
Question: **What formulation do you use?**

Amphotericin B 5 mcg/0.1 mL intravitreal inj. Injected by physician during surgery
Amphotericin B 5 mcg/0.1 mL intravitreal inj.
For injection by physician during surgery

You are inspecting the syringe prepared by the compounding technician, do you accept it?
Objective 1

• Review the anatomy of the eye to distinguish the requirements of compounded preparations for each unique site of administration.
Compounding Ophthalmic Preparations

1. Eye Anatomy
   - Injection sites of Ophthalmic Preparations
   - Requirements for Ophthalmic Preparations

2. Master Formula Requirements
   - Research and References to Use
   - Important Factors to Consider
   - Writing a Master Formula

3. Review Compounding Staff’s Education
   - Example Drug Errors and Avoidance
   - Education for the Staff and the Patient
Anatomy of the Eye

- Cornea
- Epithelium
- Bowman's membrane
- Stroma
- Descemet's membrane
- Endothelium
- Pupillary sphincter muscle
- Iris
- Anterior chamber
- Lateral rectus muscle
- Sclera
- Fovea centralis
- Optic disk
- Central retinal artery
- Central retinal vein
- Retina
- Medial rectus muscle
- Lens
- Posterior chamber
- Trabecular meshwork

Ophthalmic Administration Locations

**TOPICAL:**
- Ointments (1 – 5)
- Drops (3 – 5)

**INJECTION:**
- Subconjunctival (5 – 6)
- Deep subtenons (6 – 8)
- Retrobulbar (8)

Ophthalmic Administration: **Intraocular**

- Injected into the **anterior chamber** or **vitreous chamber**
- Requires solution sterility, non-pyrogenicity, no particulates
- May require sterility of the external package (syringe) during surgery
- Required to be preservative free
- Manufactured products include miotics, viscoelastics, and antivirals for CMV retinitis.

Ophthalmic Administration: **Intracameral**

- Injected into the **anterior chamber**:
  - Acetylcholine chloride
  - Alpha-chymotrypsin
  - Carbamylcholine chloride
  - Certain antibiotics
  - Certain steroids

- Commonly compounded by pharmacy
Ophthalmic Administration: **Intravitreal**

- Injected into the *vitreous chamber*:
  - Antifungals
  - Antibiotics
  - Certain steroids

- Commonly compounded by pharmacy

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Ophthalmic Administration: Peri-ocular

- Peri-ocular locations include:
  - Subconjunctival
  - Peribulbar
  - Retrobulbar

- Sometimes required when topical drug penetration is not optimal

- Typically inject antibiotics, steroids, and local anaesthetics through these routes.

**Ophthalmic Administration: Subconjunctival**

- **Subconjunctival** used for medications with poor absorption if applied topically.
- Injected underneath subconjunctival tissue; drug is then passed through the sclera and into the eye via simple diffusion.
- Most commonly for antibiotics for infections of anterior eye segment.
- Mydriatics and cycloplegics used to achieve pupillary dilation and relaxation of ciliary muscle.

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Ophthalmic Administration: Peri-bulbar

• **Peribulbar** (outer sides of eye)
  • This area is not well vascularized thus less chance of drug removal from blood flow
  • Local anaesthetics spread to eye lid and surrounding spaces
  • Typical injections are local anaesthetics, enzymes with local anaesthetics, steroids, vasodilators

Ophthalmic Administration: Retrobulbar

- **Retrobulbar** space (back of eye)
- Injected into muscle cone to block nerve ganglion, cranial nerves III, IV, V
- This area is not well vascularized thus less chance of drug removal from blood flow
- Typical injections are antibiotics, local anaesthetics, enzymes with local anaesthetics, steroids, vasodilators

Ophthalmic Administration: **Irrigations**

- Typically used in surgery to maintain hydration, ocular volume, and clarity of the cornea (made for topical and intraocular use)
- Provides physiological medium for removing blood and debris, and replaces natural aqueous intraocular fluid, **pH = 7.4**
- Balanced salt solution (BSS) is the primary irrigating fluid
- BSS contains sodium, potassium, calcium, magnesium, chloride, with pH of neutral to slight alkaline, osmolarity is 305 mOsm/kg
- Enriched BSS is also available (includes oxidized glutathione, dextrose, bicarbonate, and other ions)

Pharmacist’s Role: What to Know!

- Be prepared to make these preparations:
  - Non-commercial products
  - Preservative free versions of manufactured products
  - Pediatric strengths if needed (special orders)
- Know the basics of ocular infections (locations, organisms).
- Know the drug dosing (evidence-based but off-label).
- Know the appropriate compounding procedures.
- Know the concentration and frequency of use.
- Become the expert in your pharmacy!
Pharmacist’s Role: Ocular Infections

• **Organisms**: bacteria, viruses, fungi, protozoa

• **Typical infection locations**:
  • Conjunctivitis
  • Keratitis
  • Uveitis
  • Retinitis
  • Endophthalmitis
Pharmacist’s Role: **Dosing & Concentration**

- **Dosing**: evidence-based, off-label
- Where to get dosing information if off-label?
- Where to get concentration of final product?
Example: Orders for Bacterial Endophthalmitis

**Intravitreal Injections:**

- Vancomycin 0.1 mg/0.1 mL
- Ceftazidime 2.25 mg/0.1 mL (or Amikacin 0.4 mg/0.1 mL)
- Dexamethasone 0.4 mg/0.1 mL

**Topical Drops:**

- Vancomycin 25 mg/mL every 1 hour
- Ceftazidime 50 mg/mL every 1 hour
- Topical steroids (manufactured product, no compounding)
Dispensing Compounded Topical Eye Drops

• **CASE:** Patient is presenting to the emergency room for endophthalmitis and prescribed fortified antibiotic eye drops until he can be seen by the ophthalmologist in 2 days. The eye drop order is for 1 drop in the left eye every 1 hour.

• Is the patient able to acquire these outside of the hospital?
• Does the hospital pharmacist need to prepare enough for the full course of therapy?
• Typical eye dropper: 1 mL contains 20 drops
Objective 2

• Construct master formulas for sterile ophthalmic preparations.
Compounding Ophthalmic Preparations

1. Eye Anatomy
   • Injection sites of Ophthalmic Preparations
   • Requirements for Ophthalmic Preparations

2. Master Formula Requirements
   • Research and References to Use
   • Important Factors to Consider
   • Writing a Master Formula

3. Review Compounding Staff’s Education
   • Example Drug Errors and Avoidance
   • Education for the Staff and the Patient
Master Formula Requirements (USP 797)

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- Type and size of container—closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP (quality review)
- BUD and storage requirements
- Reference source to support the stability of the CSP

If applicable, the Master Formulation Record must also include:

- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Sterilization method (e.g., steam, dry heat, irradiation, or filter)
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and toxicity)

Ceftazidime 22.5 mg/1 mL Intravitreal Injection Syringe

**Compounded with Preservative Free Ingredients & Solutions.**

<table>
<thead>
<tr>
<th>Compounding Ingredients (Active + Inactive) and Supplies</th>
<th>Sample Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime in the available dosage vials: 1 Gram vial</td>
<td>Ceftazidime (Fortaz) 22.5 mg/1 mL</td>
</tr>
<tr>
<td>Sterile water for injection (SWFI) preservative free (PF): 20 mL vial</td>
<td>Prep: ____, Exp: ____, Lot: ____, FROZEN EXP:</td>
</tr>
<tr>
<td>Sodium chloride (NS) for injection preservative free (PF): 10 mL vial</td>
<td></td>
</tr>
<tr>
<td>Sterile empty container (10 mL or greater)</td>
<td></td>
</tr>
<tr>
<td>Syringes of appropriate size: 1 mL, 10 mL</td>
<td></td>
</tr>
<tr>
<td>Filter needle(s) (5-micron), regular needles of appropriate size</td>
<td></td>
</tr>
<tr>
<td>Syringe caps (snap or luer lock)</td>
<td></td>
</tr>
</tbody>
</table>

**USP 797 Beyond Use Date (BUD):**

- Drug Physical/Chemical Stability
- Equipment & Environmental BUD Limitations / Hazardous Drug Compounding Requirements

**Non-Hazardous Drugs:**

- CAI (compounding aseptic isolator), CACI, or laminar flow hood
- Hazardous Drugs: CACI (compounding aseptic containment isolator) – “glove-box hood”

**Beyond Use Date Limits:** Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area. A 12 hour maximum BUD limitation is applied when sterile products are compounded in ISO-5 environments within a segregated compounding area (not meeting ISO-7 air quality or 30 air changes per hour) or when the compounding area is undergoing environmental remediation. A 1 hour maximum BUD limitation is applied when the compounding area does not meet the minimum USP 797 environmental standards.

**Compounding Procedure**

1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PF* NS (conc. = 50 mg/mL) vial has overfill.
2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PF* NS (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL), or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).
3. Inject the dilution through a 5-micron filter-needle into a sterile empty container.
4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (> 22.5 mg/mL) volume into a 1 mL syringe and seal with a syringe cap.
5. This makes 44 x 1 mL syringes or 2 syringes, label as indicated and store in freezer; thaw before use.

**Dispensing Notes / Logistical Notes**

- Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.
- 1.5 hours for 44 syringes 10 min for 2 syringes

**Quality Reviews During Compounding & Final Dispensing**

1. SOURCES: In the absence of particulates, foreign bodies, chemical incompatibility, precipitation, appropriate size - sterile, colorless
2. CONTAMINANTS: cover placement of caps, seals, crimps, port covers, container box components, labels, or other visible damage.
3. PRODUCT: Final compounded meets the oriented components, required initial and final diluents, final volume and final concentration.
4. STORAGE & BUD: starting components were stored correctly, final compounded product labeled for correct storage conditions and BUD.
5. AUREC: labels are clear, barcodes clear, compounding lot included, storage conditions and BUD/expiration dates are visible.
6. ORDER/PAYMENTS: appropriatenotationofcompoundingpersonnelinvolvedintheprocesswithfinalapprovalbythe pharmacist.

**References for Compounding, Drug Stability, BUD Classifications**

- ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products 2018; Clinical Pharmacology 2018
- Flynn H, Recognition, Treatment and Prevention of Endophthalmitis 2016
Compounding Record Requirements (USP 797)

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- Identity of all individuals involved in each step (e.g., technician or pharmacist)
- Name, vendor or manufacturer, lot number, and expiration date for each ingredient
- Weight or volume of each ingredient
- Total quantity compounded
- Assigned BUD and storage requirements
- If applicable, the Compounding Record must also include:
  - Master Formulation Record reference for the CSP
  - Calculations made to determine and verify quantities and/or concentrations of components
  - Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)
Building Your Ophthalmic Master Formula

• You will need:
  • References (books, journals, etc.)
  • Attention to detail (reading and writing)
  • Master formula template
  • Second reviewer
### Compounding & Stability References

**Trissel, Handbook on Injectable Drugs. 19th Edition**
- ISBN: 978-1585285594
- Drug compatibility in solution, with additives
- Drugs in syringe compatibility
- Y-site injection compatibility (1:1 mixture)

<table>
<thead>
<tr>
<th>Monograph drug name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution Mfr Mfr Conc/L Remarks Ref C/I</td>
</tr>
<tr>
<td>(1) (2) (3) (4) (5) (6) (7)</td>
</tr>
</tbody>
</table>

- Solution in which the test was conducted.
- Manufacturer of the solution.
- Manufacturer of the drug about which the monograph is written.
- Concentration of the drug about which the monograph is written.
- Description of the results of the test.
- Reference to the original source of the information.
- Designation of the compatibility (C) or incompatibility (I) of the test result according to conventional guidelines.
Bing and Nowobilski-Vasilios, Extended Stability for Parenteral Drugs, 6th Edition

- Covers all aspects of determining stability, including the changing elastomeric landscape and the ongoing variability in stability data.
- Nearly all 165 stability monographs completely updated
- Updated chapters on applying stability data in patient care and parenteral nutrition
- Previously unpublished data for specific types of infusion devices and containers Direct communications from drug and device manufacturers, and a focused review of previously published data from practitioners.

https://store.ashp.org/Store/ProductListing/ProductDetails.aspx?productId=597629135
Compounding & Stability References

Trissel’s Stability of Compounded Formulations, 6th Edition

- ISBN: 978-1582122960
- Compiles all currently available stability information on drugs in compounded oral, enteral, topical, ophthalmic, and other specialized preparations. It includes monographs on 571 products, including 61 new monographs and 163 monographs
- Each monograph organized categories: Properties, General Stability Considerations, Stability Reports of Compounded Preparations, including repackaging information, Compatibility with Other Drugs and Compatibility with Common Beverages and Foods
- Summaries from 2,043 published articles and books, including 329 new to this edition
- Index of nonproprietary and brand names

https://ebusiness.pharmacist.com/PersonifyEbusiness/Shop-APhA/Product-Details/productId/286040071
Lexi-Comp Drug Information Handbook (and phone app)

- ISBN: 978-1-59195-370-8
- This handbook follows a dictionary-like format, with drug products organized alphabetically and cross-referenced by U.S. and Canadian brand names and index terms.
- Contains 1600 drug monographs, each offering up to 45 fields of information specific to a particular medication.
- Appendix offering helpful treatment guidelines and therapy recommendations, and a Pharmacologic Category Index.
- 1696 Drug Monographs, with up to 45 fields of information
- More than 50 Pages of Appendix Information
AHFS Drug Information Handbook


• Information is evidence-based, reviewed by subject matter experts, and supported by nearly 90,000 references. Every year’s edition is updated with an expanded number of monographs:

• Interactions, adverse reactions, and cautions, including ongoing revisions addressing opiate safety issues and their role in pain management.

• Extensive dosage and administration information.

• Pharmacology and pharmacokinetics.

• Prescription, OTC, opthalmic, and dermatologic drugs.

• Extensive off-label uses and related dosing options.

http://www.ahfsdruginformation.com/ahfs-drug-information/
Nahata MC, Pai BV. Pediatric Drug Formulations, 7th Edition

- ISBN: 978-0-929375-12-0
- 540 Extemporaneous Formulas
- Multiple Formulas of Certain Drugs
- Pediatric Oral Formulations
- Nasal Inhalations
- Ophthalmic Topical Formulations
- Ingredients
- Preparation Instructions
- Storage Conditions
- Stability References

- Oral Elixir/Solution/Suspension/Syrups
- Topical/Ophthalmic Solutions
- Commercially Available Products
- Ingredients & Preparation Instructions
- Storage Conditions; Specials Instructions
- Storage Container Type(s)
- Expiration Dates
- References
General Guidelines & Resources

• USP Compendium USP40-NF35 (2017): USP 797, USP 800
• USP 771 Ophthalmic Preparations
• NIOSH List of Hazardous Drugs
• Institute for Safe Medication Practices (ISMP)
• ASHP Guidelines on Compounding Sterile Preparations
• ASHP Guidelines on Quality Assurance for Pharmacy Sterile Products
• ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products
• Local and National Regulations
Compounding & Stability Resources

• Trissel’s Stability of Compounded Formulations
• Trissel’s Handbook on Injectable
• Trissel's’ Clinical Pharmaceutics Database
• King Guide to Parenteral Admixtures
• Extended Stability of Parenteral Drugs (Bing)
• American Journal of Hospital Pharmacy (AJHP)
• Published ophthalmic compounding drug stability studies
Ophthalmic Journals

• Journal of the American Medical Association (JAMA): Ophthalmology
• Journal of Clinical & Experimental Ophthalmology
• American Journal of Ophthalmology
• British Journal of Ophthalmology
• Saudi Journal of Ophthalmology
• Middle East African Journal of Ophthalmology
• Annals of Ophthalmology
• Case Reports in Ophthalmology
• MANY MORE: https://www.omicsonline.org/ophthalmology-journals-conferences-list.php
USP 771: Ophthalmic Preparations

- Anatomy of the Eye (nice pictures)
- Routes of Administration: Topical, Systemic, Periocular, Intravitreal
- Dosage Forms Applied to the Eye: Suspensions, Ointments, Gels, Emulsions, Strips, Injections, Inserts, Contact Lenses, Implants, Colloidal Systems, Microemulsions, Nanosuspensions, Hydrogels
- Container Closure Systems
- Drug Product Quality Tests: Assay, pH, Osmolarity, Particulates, Viscosity, Drop Sizes
- Sterility and Antimicrobial Preservatives
Pharmacist’s Role: **Writing Master Formulas**

- Review the requirements of compounded ophthalmic preparations:
  - **Sterility** (for both injectable and topical preparations)
  - **Osmolarity** (ideal: 300 mOsmol/L; tolerated: 200 – 600 mOsmol/L)
  - **pH near 7.4** (considered for drug stability and patient comfort)
  - **Filtration** (if compounded from a powder, or from glass ampule)
  - **Solubility** and **stability** in an appropriate vehicle
  - **Diluents** (SWFI, NS, BSS, LR, artificial tears)
  - **Final concentration** and **viscosity**
  - **Preservative content**
  - **Packaging** (light protect, oxygen protection before/after opening)

 Felton 2013, McElhiney 2013, ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products
Compounding: Powder Volume (Displacement)

• Write the master formula to account for powder displacements

EXAMPLE:
• Cefotaxime has a displacement value of 0.2 mL per 500 mg vial
• If 2 mL of SWI is added, the final concentration = 500 mg/2.2 mL
• Add 1.8 mL of SWFI, then final concentration = 500 mg/2 mL

• Many compounding formulas forget to account for this
• Review package inserts for this (check intramuscular section):
  • If not able to find the displacement value, what can you do?
Compounding: Powder Volume (Displacement)

If not able to find the displacement value, what can you do?

• **SOLUTION**: Dilute the drug with a smaller amount, then pull all solution back into the syringe, and then QS the syringe up to the required volume for the formula.

• **EXCEPTION**: if the drug has extra powder in it already to account for fluid overfill after dilution... then you must compound based on the package insert to the known concentration, then withdraw what you need and do further serial dilutions.

Check package inserts for this information
Compounding: **Syringe & Needle Dead Space**

- The “dead space” affects the final presentation of the preparation.
- **EXAMPLE (dose):** 0.2 mg/0.2 mL
- **EXAMPLE (product sent):** 0.5 mg/0.5 mL in a 1 mL syringe
- Final presentation of the product should be consistent and best described in the master formula
Compounding: Using Filters

• When diluting powders for ophthalmic use, it is essential to filter the reconstituted drug.

• FILTER REQUIRED!

• Not all drugs should be filtered (bevacizumab)
Compounding: ISMP Safety Best Practices

• At a minimum, perform an independent verification for all:
  • High-alert medications (including chemotherapy and parenteral nutrition)
  • Pediatric/Neonatal preparations
  • Pharmacy-prepared source/bulk containers
  • Products administered via high-risk routes of administration (e.g., intrathecal, epidural, intraocular), and
  • Other compounded sterile preparations that the organization believes are high-risk.

• Independent verification: ensuring correct ingredients (medications, diluents), and correct volumes added at each step prior to addition to the final container.
Master Formula: Ceftazidime 22.5 mg/1 mL

Title & Compounding Ingredients & Supplies

- The title lists the drug/volume of the entire product, which may differ from the intended dose
- Compound product: 22.5 mg/1 mL
- Intended dose: 2.25 mg/0.1 mL
- Ceftazidime in the available dosage vial(s): 1 Gram vial
- SWFI preservative free (PF) : 20 mL vial
- Syringe caps (snap or luer lock)
- Syringes of appropriate size: 1 mL, 10 mL
- Sterile empty container (10 mL or greater)
- Syringes of an appropriate size: 1 mL, 10 mL
- Filter needle(s) (5-micron), regular needles of appropriate size
- Syringe caps (snap or luer lock)

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Ceftazidime 22.5 mg/1 mL Intravitreal Injection Syringe

Compounded with Preservative Free Ingredients & Solutions.

<table>
<thead>
<tr>
<th>Sample Label</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime (Fortaz) 22.5 mg/mL</td>
<td>Ceftazidime (Fortaz) 22.5 mg/mL</td>
</tr>
<tr>
<td>Lot: _________________</td>
<td>Lot: _________________</td>
</tr>
<tr>
<td>FROZEN EXP:</td>
<td>FROZEN EXP:</td>
</tr>
</tbody>
</table>

Final Weight or Volume

USP 797 Beyond Use Date (BUD)

<table>
<thead>
<tr>
<th>Drug Identity/Clinical Setting</th>
<th>Hazardous Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 days frozen</td>
<td>Non-Hazardous</td>
</tr>
<tr>
<td>9 days refrigerated (NTE 45 day BUD)</td>
<td>Non-Hazardous</td>
</tr>
<tr>
<td>7 – 168 days refrigerated (references)</td>
<td>Non-Hazardous</td>
</tr>
<tr>
<td>24 hours room temperature</td>
<td>Non-Hazardous</td>
</tr>
</tbody>
</table>

Equipment & Environmental BUD Limitations / Hazardous Drug Compounding Requirements

- Non-Hazardous Drugs: CAG (compounding aseptic isolator), CACI, or laminar flow hood
- Hazardous Drugs: CAGI (compounding aseptic containment isolator) – "glove-box hood"

Beyond Use Date Limits: Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area. A 12 hour maximum BUD limitation is applied when sterile products are compounded in ISO-5 environments within a segregated compounding area (not meeting ISO 7 or quality or 30 air changes per hour) or when the compounding area is undergoing environmental remediation. A 4 hour maximum BUD limitation is applied when the compounding area does not meet the minimum USP 797 environmental standards.

Compounding Procedure

1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PF* NS (conc. = 50 mg/mL) vial has overfill.
2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PF* NS (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL), or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).
3. Inject the dilution through a 5-micron filter-needle into a sterile empty container.
4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (= 22.5 mg) volume into a 1 mL syringe and seal with a syringe cap.
5. This makes 44 x 1 mL syringes (or 2 syringes), label as indicated and store in freezer; thaw before use.

Dispensing Notes / Logistical Notes

- Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.
- 1.5 Hours for 44 syringes 10 min for 2 syringes

Quality Reviews During Compounding & Final Dispensing

1. IDENTIFICATION: no evidence of particulates, foreign bodies, chemical incompatibility, precipitation, appropriate color – clear, colorless
2. CONTAMINATION: correct placement of caps, seals, crimps, port covers, container box components, labels, or other visible damage
3. PRODUCT: final compounded reaches the ordered components, required initial and final diluents, final volume and final concentration.
4. STORABILITY: all compounded products were stored correctly, final compounded product labeled for correct storage conditions and BUD.
5. LABELS: are clear, barcodes clear, compounding lot included, storage conditions and BUD/expiration dates are visible.
6. PRODUCT APPROVALS: appropriate manufacture of compounded personnel involved in the process with final approval by the pharmacist.

References for Compounding, Drug Stability, BUD Classifications

6. Flynn H, Recognition, Treatment and Prevention of Endophthalmitis 2017

www.ivpnsymposium.org

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**Beyond Use Date & Physical/Chemical Stability**

- **USP 797 Beyond Use Date (BUD) – 2017**
  - 45 days frozen
  - 9 days refrigerated (NTE 45 day Frozen BUD)
  - 24 hr room temp (NTE 45 day Frozen BUD)
- **Drug Physical/Chemical Stability**
  - 168 days frozen (references)
  - 7 – 168 days refrigerated (references)
  - 24 hours room temperature
Can we use the same BUD as drugs prepared for intravenous use?

a. Yes
b. No
Can we use the same BUD as drugs prepared for intravenous use?

a. Yes

b. No

WHY?

• Concentrations are different
• Reconstitution solutions may differ (SWFI, NS, D5W, BSS, LR)
• Storage container is different (syringe vs IVPB)
• Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area.

• A 12 hour maximum BUD limitation is applied when sterile products are compounded in ISO-5 environments within a segregated compounding area (not meeting ISO-7 air quality or 30 air changes per hour) or when the compounding area is undergoing environmental remediation. (or 24 HR in draft 797)

• A 1 hour maximum BUD limitation is applied when the compounding area does not meet the minimum USP 797 environmental standards.

Master Formula: Ceftazidime 22.5 mg/1 mL

Equipment & Environmental BUD Limitations

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<td>Ceftazidime (Fortaz)</td>
</tr>
<tr>
<td>Sterile water for injection (SWFI) preservative free (PF) : 20 mL vial</td>
<td>22.5 mg/mL</td>
</tr>
<tr>
<td>Sodium chloride (NS) for injection preservative free (PF) : 10 mL vial</td>
<td>Prep. Exp.</td>
</tr>
<tr>
<td>Sterile empty container (10 mL or greater)</td>
<td>Lot:</td>
</tr>
<tr>
<td>Syringes of appropriate size: 1 mL, 10 mL</td>
<td>FROZEN EXP:</td>
</tr>
<tr>
<td>Filter needle(s) (5-micron), regular needles of appropriate size</td>
<td>Final Weight or Volume</td>
</tr>
<tr>
<td>Syringe caps (snap or luer lock)</td>
<td>1 mL or 10 mL syringe</td>
</tr>
</tbody>
</table>

USP 797 Beyond Use Date (BUD) | Drug Physical/Chemical Stability | Hazardous Classification |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>45 days frozen</td>
<td>168 days refrigerated (NTE 45 day BUD)</td>
<td>Non-Hazardous</td>
</tr>
<tr>
<td>17 – 168 days refrigerated (references)</td>
<td>Hazardous Classification</td>
<td></td>
</tr>
</tbody>
</table>

Equipment & Environmental BUD Limitations // Hazardous Drug Compounding Requirements

- Non-Hazardous Drug: CAI (compounding aseptic isolator), CAI, or laminar flow hood
- Hazardous Drug: CAI (compounding aseptic containment isolation) – “glove-box hood”

Beyond Use Date Limits: Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area. A 12 hour maximum BUD limitation is applied when sterile products are compounded in ISO-5 environments within a segregated compounding area (not meeting ISO-7 air quality or 30 air changes per hour) or when the compounding area is undergoing environmental remediation. A 1 hour maximum BUD limitation is applied when the compounding area does not meet the maximum USP 797 environmental standards.

Compounding Procedure:
1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PF* NS (conc. = 50 mg/mL) vial has overfill.
2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PF* NS (new conc = 1000 mg/44.4 mL = 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc = 22.5 mg/mL).
3. Inject the dilution through a 5-micron filter-needle into a sterile empty container.
4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (> 22.5 mg) volume into a 1 mL syringe and seal with a syringe cap.
5. This makes 44 x 1 mL syringes (or 2 syringes), label as indicated and store in freezer; thaw before use.

Dispensing Notes / Ingotatal Notes

- Compounding Time
- Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.
- 1.5 hours for 44 syringes
- 10 min for 2 syringes

Quality Reviews During Compounding & Final Dispensing

1. AUDITORS: no evidence of particulates, foreign bodies, chemical incompatibility, precipitation, inappropriate color - ’white, clear.
2. CONTAINS: correct placement of caps, seals, caps, caps, paper covers, container box, excipients, seal, or other visible damage.
3. PRODUCT: final compounded matches the labeled, intended and final diluted, final volume and final concentration.
4. STORAGE & BUD: storage compartments were sealed correctly.
5. LABELS: labels are clear, barcodes clear, compounding lot included, storage conditions and BUD/expiration dates are visible.
6. PRODUCT APPROVAL: atopical contamination of compounded personnel involved in the process with final approval by the pharmacist.

References for Compounding, Drug Stability, BUD Classifications

- ASHP Guidelines on Pharmacy Practice: Aseptic Compounding in the Health Care Setting, 2018 edition (accessed 1/16/18)
- Flynn H, Recognition, Treatment and Prevention of Endophthalmitis. Retina 2011;31:1316
- United States Pharmacopeia General Chapter <797> [USP40/NF35] 2017
- Manufacturer’s Recommendation & Package Insert; Lexi-Comp Online 2018; Clinical Pharmacology 2018; Micromedex 2018
- Hazardous Drugs: CACI (compounding aseptic containment isolation) – “glove-box hood”
- CAI (compounding aseptic isolator), CACI, or laminar flow hood
- Beyond Use Date Limits: Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area. A 12 hour maximum BUD limitation is applied when sterile products are compounded in ISO-5 environments within a segregated compounding area (not meeting ISO-7 air quality or 30 air changes per hour) or when the compounding area is undergoing environmental remediation. A 1 hour maximum BUD limitation is applied when the compounding area does not meet the maximum USP 797 environmental standards.
Ceftazidime 22.5 mg/1 mL Intravitreal Injection Syringe
Compounded with Preservative Free Ingredients & Solutions.

Compounding Procedure

1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PF* NS (conc. = 50 mg/mL); vial has overfill.

2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PF* NS (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).

3. Inject the dilution through a 5-micron filter-needle into a sterile empty container.

4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (= 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of NS (*PF*) (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).

5. This makes 44 x 1 mL syringes.

6. Label as indicated and store in freezer; thaw before use.

References for Compounding, Drug Stability, BUD Classifications

Micromedex 2018

Micromedex.com

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USP-NF General Chapter <797> [USP39/NF34]

Template © Michael Freudiger 2017
Dispensing Notes: Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center. Make as 1 mL in a 1 mL Syringe

Compounding Time:
• 1.5 hours for 44 syringes
• 10 min for 2 syringes

Sample Label: (labeling the product, not the dose)
**Master Formula: Ceftazidime 22.5 mg/1 mL**

**Quality Reviews: Compounding & Fina Dispensing**

- **SOLUTION**: no evidence of particulates, foreign bodies, chemical incompatibility, precipitation, appropriate color = clear, colorless
- **CONTAINER**: correct placement of all caps, seals, crimps, port covers; container has no punctures, leaks, or other visible damage.
- **PRODUCT**: final compound matches the ordered components, required initial and final diluents, final volume and final concentration.
- **STORAGE & BUD**: starting components were stored correctly, final compounded product labeled for correct storage conditions and BUD.
- **LABELS**: labels are clear, barcodes clean, compounding lot #s included, storage conditions and BUD/expiration dates are visible.

**PRODUCT APPROVAL**: signatures/documentation of compounding personnel involved in the process with final approval by the pharmacist.

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**Ceftazidime 22.5 mg/1 mL Intravitreal Injection Syringe**

**Compounded with Preservative Free Ingredients & Solutions.**

**Compounding ingredients (Active + Inactive) and Supplies**

<table>
<thead>
<tr>
<th>Component</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime powder</td>
<td>-</td>
</tr>
<tr>
<td>Sterile water for injection (SWFI)</td>
<td>-</td>
</tr>
<tr>
<td>Sodium chloride (NS)</td>
<td>-</td>
</tr>
<tr>
<td>Sterile bottles</td>
<td>-</td>
</tr>
<tr>
<td>Filter needle (5-micron)</td>
<td>-</td>
</tr>
<tr>
<td>Syringe caps</td>
<td>-</td>
</tr>
<tr>
<td>Syringe</td>
<td>-</td>
</tr>
</tbody>
</table>

**Compounding Procedure**

1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PP* NS (conc. = 50 mg/mL); vial has overfill.
2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PP* NS (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PP* NS (new conc. = 22.5 mg/mL).
3. Inject the dilution through a 5-micron filter-needle into a sterile empty container.
4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (= 22.5 mg) volume into a 1 mL syringe and seal with a syringe cap.
5. This makes 44 x 1 mL syringes (or 2 syringes), label as indicated and store in freezer; thaw before use.

**Dispensing Notes/Logistical Notes**

- Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.
-umble after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.
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- Freeze after preparation, store in main pharmacy freezer until delivered to ophthalmic surgical center.

**Compounding Time**

1. Dilution: no evidence of particulates, foreign bodies, chemical incompatibility, precipitation, appropriate color = clear, colorless
2. CONTAINER: correct placement of all caps, seals, crimps, port covers; container has no punctures, leaks, or other visible damage.
3. PRODUCT: final compound matches the ordered components, required initial and final diluents, final volume and final concentration.
4. STORAGE & BUD: starting components were stored correctly, final compounded product labeled for correct storage conditions and BUD.
5. LABELS: labels are clear, barcodes clean, compounding lot #s included, storage conditions and BUD/expiration dates are visible.

**Product Approvals**

- Product Approvals: signatures/documentation of compounding personnel involved in the process with final approval by the pharmacist.

---

**USP-NF General Chapter <797> [USP39/NF34]**

www.ivpnsymposium.org
Master Formula: Ceftazidime 22.5 mg/1 mL
Notes: decisions based on references

- Not listed in my example, but this is either part of a “Notes” section of the master formula itself or it is just your compounding journal of notes during the formula construction process.
- A file folder would also contain the references you found and can easily refer to if you need it later.

KEEP GOOD RECORDS OF EVERYTHING!

SAVE EVERYTHING!

---

**Ceftazidime 22.5 mg/1 mL Intravitreal Injection Syringe**

*Compounded with Preservative Free Ingredients & Solutions.*

**Compounding ingredients (Active + Inactive) and Supplies**

**Sample Label**

- Ceftazidime in the available dosage (vial): 1 Gram vial
- Sterile water for injection (SWF): 20 mL vial
- Sodium chloride (NS): 10 mL vial
- Sterile empty container (10 mL or greater)
- Syringes of appropriate size: 1 mL, 10 mL
- Filter needle(s) (5-micron), regular needles of appropriate size
- Syringe caps (snap or luer lock)

**USP 797 Beyond Use Date (BUD) & Drug Physical/Chemical Stability**

- Hazardous Classification
  - Hazardous Drugs: C-AI (compounding aseptic isolator), C-AI, laminar flow hood
  - Beyond Use Date Limit: Maximum BUD as listed above are applicable only if the sterile product is compounded in an ISO-5 environment within an ISO-7 area. A 12 hour maximum BUD limitation is applied when sterile products are compounded in an ISO-7 environment within a segregated compounding area (not meeting ISO-5 or quality or ISO 30 air changes per hour) or when the compounding area is undergoing environmental remediation. A 1 hour maximum BUD limitation is applied when the compounding area does not meet the minimum USP 797 environmental standards.

**Compounding Procedure**

1. Dilute a ceftazidime 1 gram powder vial with 20.6 mL of *PF* NS (conc. = 50 mg/mL).
2. Withdraw 20 mL (conc. 50 mg/mL) ceftazidime and add 24.4 mL of *PF* NS (new conc. = 1000 mg/44.4 mL = 22.5 mg/mL), or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).
3. Inject the dilution through a 5-micron filter into a sterile empty container.
4. Attach the appropriate connector or pin to the sterile container and withdraw 1 mL (= 22.5 mg/mL); or to make 2 syringes, withdraw 1 mL (conc. 50 mg/mL) ceftazidime and add 1.22 mL of *PF* NS (new conc. = 22.5 mg/mL).
5. This makes 44 x 1 mL syringes (or 2 syringes).

**Compounding Time**

- 1.5 Hours for 44 syringes
- 10 min for 2 syringes

**Quality Reviews During Compounding & Final Dispensing**

1. OUTSIDE: no evidence of particulates, foreign bodies, chemical incompatibility, precipitation, appropriate size - (size, needle)
2. CONTAINER: correct placement of all caps, seals, crimps, port covers, container box unreopened, seal, or other visible damage.
3. PRODUCT: final compounded meets the ordered components, required initial and final diluents, final volume and final concentration.
4. STORAGE & BUD: storage parameters and expiration times for current storage conditions and BUD.
5. LABELS: labels are clear, barcodes clean, compounding lot included, storage conditions and BUD/expiration dates are visible.
6. PRODUCT: RHBDs, documentation of environmental remediation of the process with final approval by the pharmacist.

**References for Compounding, Drug Stability, BUD Classifications**

- Cady J, Recognition, Treatment and Prevention of Endophthalmitis. Retina 2011;31:1160-1182
- Flynn H, Recognition, Treatment and Prevention of Endophthalmitis 2016
- INO Guideline on Hypromellose-Optimized Products. 2009
- Just an idea…
- www.ivpn symposium.org

Template © Michael Freudiger 2017
Ophthalmic Injections: Frequent Preparations

- Amikacin 0.4 mg/0.1 mL intravitreal injection
- Amphotericin B (conventional) 5 mcg/0.1 mL intravitreal injection
- Cefazolin 100 mg/0.5 mL intravitreal injection
- Ceftazidime 2 mg/0.1 mL intravitreal injection
- Ceftazidime 2.25 mg/0.1 mL intravitreal injection
- Cidofovir 20 mcg/0.1 mL intravitreal injection
- Dexamethasone 0.4 mg/0.1 mL intravitreal injection
- Foscarnet 2.4 mg/0.1 mL intravitreal injection
- Ganciclovir 2 mg/0.1 mL intravitreal injection
- Gentamicin 200 mcg/0.1 mL intravitreal injection
- Vancomycin 1 mg/0.1 mL intravitreal injection
- Vancomycin 2 mg/0.1 mL intravitreal injection
- Voriconazole 100 mcg/0.1 mL intravitreal injection
Intravitreal Injection:

**Ceftazidime 2.25 mg/0.1 mL**

1. Begin with 500 mg vial of Ceftazidime (this is a powder).
2. Add 9.2 mL of 0.9% Sodium Chloride for Injection, USP (no preservatives) (or BSS) to 500 mg vial in #1.
3. Inject 1 mL of the solution #2 into an empty sterile vial using a 5-micron FILTER NEEDLE.
4. Add 1.2 mL of Sodium Chloride for Injection, USP (no preservatives) into the vial #2 to produce a solution containing 2.25 mg/0.1 mL ceftazidime.
5. Send the preparation as 0.5 mL into a 1 mL syringe.
6. Stability = 9 days FR; 24 hours RT

Flynn HW, Relhan N. Recognition, Treatment and Prevention of Endophthalmitis. University of Miami School of Medicine. 2016
Intravitreal Injection:
Vancomycin 1 mg/0.1 mL

1. Begin with 500 mg vial of Vancomycin (this is a powder).
2. Add 10 mL of 0.9% Sodium Chloride for Injection, USP (no preservatives) (or BSS) to 500 mg vial in #1.
3. Inject 2 mL of solution #2 into a sterile empty vial using a 5-micron FILTER NEEDLE.
4. Add 8 mL of 0.9% Sodium Chloride for Injection, USP (no preservative) (or BSS) to produce a solution containing vancomycin 1 mg/0.1 mL.
5. Send the preparation as 0.5 mL into a 1 mL syringe.
6. Stability = 9 days FR; 30 hours RT

 Flynn HW, Relhan N. Recognition, Treatment and Prevention of Endophthalmitis. University of Miami School of Medicine. 2016
Intravitreal Injection:
Amikacin 0.4 mg/0.1 mL

1. Begin with 500 mg/2 mL vial of amikacin (250 mg/mL)
2. Inject 0.16 mL of solution #1 (40 mg) into sterile empty vial (filter needle not requires as this is a drug in solution)
3. Add 9.84 mL of 0.9% Sodium Chloride Injection, USP (no preservatives to produce a solution of 0.4 mg/0.1 mL amikacin)
4. Send the preparation as 0.5 mL into a 1 mL syringe.
5. Stability = 7 days FR; 24 hours RT
Intravitreal Injection: Amphotericin B (conventional) 5 mcg/0.1 mL

1. Begin with Amphotericin B (conventional) 50 mg vial
2. Add 10 ml of Sterile Water for Injection USP (no preservatives) to vial in #1 = 5 mg/mL
3. Inject 0.1 mL of solution #2 into a sterile empty vial using a 5-micron FILTER NEEDLE.
4. Add 9.9 ml of Sterile Water for Injection, USP (no preservatives) to vial in #3 = 0.05 mg/mL = 0.005 mg/0.1 mL = 5 mcg/0.1 mL amphotericin B
5. Send the preparation as 0.5 mL into a 1 mL syringe.
6. Stability = 9 days FR; 24 hours RT

Flynn HW, Relhan N. Recognition, Treatment and Prevention of Endophthalmitis. University of Miami School of Medicine. 2016
Intravitreal Injection:
Voriconazole 50 mcg/0.1 mL

1. Reconstitute a 200 mg vial of voriconazole powder with 19 mL of preservative-free sterile water for injection = 10 mg/mL.

2. Withdraw 1 mL (10 mg) of voriconazole solution from step 1 and q.s. to make 20 mL with preservative-free sterile water for injection = 0.5 mg/mL (500 mcg/mL).

3. Transfer the solution from step 2 in 10 mL aliquots to each of 2 sterile empty vials using a 5-micron FILTER NEEDLE.

4. Send the preparation as 0.5 mL into a 1 mL syringe.

5. Stability = 9 days FR; 30 hours RT
Intravitreal Injection:  
**Dexamethasone 0.4 mg/0.1 mL**

1. Start with the manufactured dexamethasone 4 mg/mL vial.
2. Withdraw 0.5 mL from the vial (no filter needle required)
3. Send the preparation as 0.5 mL into a 1 mL syringe.
4. Stability = 48 hours RT
1. Each syringe contains the following:
   a. Lidocaine 2% PF (5 mL)
   b. Bupivacaine 0.75% MPF (5 mL)
   c. Hyaluronidase (0.25 mL)

2. BATCH (#): Calculate the volume required of each component to prepare the batch (make 1 extra to account for losses in process)

3. Withdraw the components and combine into a sterile empty container; mix by inverting the bag repeatedly.

4. Attach the appropriate connector or pin to the sterile container and withdraw 10.25 mL into a 12 mL syringe; add syringe cap.
Retrobulbar Injection:
Local Anaesthetic Cocktail with Epinephrine

1. Each syringe contains the following:
   a. Lidocaine 2% + Epinephrine 1:100,000 PF (5 mL)
   b. Bupivacaine 0.75% + Epinephrine 1:200,000 MPF (5 mL)
   c. Hyaluronidase (0.25 mL)

2. BATCH (#): Calculate the volume required of each component to prepare the batch (make 1 extra to account for losses in process)

3. Withdraw the components and combine into a sterile empty container; mix by inverting the bag repeatedly.

4. Attach the appropriate connector or pin to the sterile container and withdraw 10.25 mL into a 12 mL syringe; add syringe cap.
Mitomycin C (surgical solution: topical)

- NOT INJECTED INTO THE EYE!
- TOPICAL use in glaucoma surgery
- Applied with a sponge for 2 minutes
- Hazardous drug
- Multiple concentrations in literature:
  - 0.1 mg/mL
  - 0.2 mg/mL ← most common
  - 0.3 mg/mL
  - 0.4 mg/mL

Fiscella 1992, Gupta 1997
Mitomycin C (surgical solution: topical)

- Mitomycin 0.2 mg/mL (1 mL in 3 mL syringe)
- Using a CSTD attached to a 30 mL syringe, withdraw 25 mL SWFI and inject into the mitomycin 5 mg vial = 0.2 mg/mL
- Withdraw the reconstituted mitomycin back into the syringe and attach a 5 micron disk filter and luer-lock to luer-lock connector.
- Attach 3 mL syringes to the connector and push a total of 1 mL of diluted/filtered mitomycin into each 3 mL syringe.

Fiscella 1992, Gupta 1997, Singh 2013
Mitomycin C (Mitosol® Kit) 0.2 mg/mL vial

Complete illustrated instructions

0.2 mg vial of mitomycin-c

Chemoclave adapters to ensure closed containment

Ziploc chemo waste bag for safe disposal

Pre-cut sponges in patented sponge tray

1mL syringe of sterile water for injection

https://mitosol.com/the-mitosol-kit/
Eye Injections: Manufactured (examples)
Which of the following must be prepared using aseptic technique?

a. Solutions for the EAR
b. Solutions for the EYE
c. Solutions for ORAL administration
d. Creams for TOPICAL administration
Which of the following must be prepared using aseptic technique?

a. Solutions for the EAR
b. Solutions for the EYE

c. Solutions for ORAL administration

d. Creams for TOPICAL administration
Topical Eye Drops: Manufactured (so many…)

- Acetylcholine 10 mg/mL solution
- Atropine 1% solution
- Betoptic S 0.25% suspension
- BSS (balanced salt solution) 15 mL
- Carbachol 0.01% solution
- Ciprofloxacin 0.3% ointment
- Cyclopentolate 0.2%/phenylephrine 1% solution
- Gentamicin 0.3% solution
- Neomycin/polymyxin/dexamethasone ointment
- Piocarpine 2% solution
- Tetracaine 0.5% solution
- Timolol 0.5% solution
- Tobramycin 0.3% solution
- Tobramycin 0.3%/dexamethasone
- Tropicamide 1% solution
Topical Eye Drops: Compounded Antibiotics (Including Fortified Eye Drops)

- Amikacin 25 – 50 mg/mL (2.5 – 5%)
- Amphotericin B (conventional) 1.5 mg/mL (0.15%)
- Bacitracin 9,600 units/mL
- Cefazolin 33 – 50 mg/mL (3.3 – 5%)
- Ceftazidime 50 mg/mL (5%)
- Colistin 1.9 mg/mL (0.19%)
- Gentamicin 13.6, 14 and 15 mg/mL (1.36, 1.4 and 1.5%)
- Imipenem/Cilastin 1 mg/mL (1%)
- Linezolid 2 mg/mL (0.2%)
- Tobramycin 13.6, 14 and 15 mg/mL (1.36, 1.4 and 1.5%)
- Vancomycin 25, 31, and 50 mg/mL (2.5, 3.1, and 5%)
- Vancomycin 50 mg/mL (5) + Amikacin 20 mg/mL (2%)
- Voriconazole 10 – 20 mg/mL (1 – 2%)

Topical Eye Drops: Fortified (Compounded)

• Fortified = making “stronger” or to a higher concentration

• Many manufactured eye drops are at 0.3% or other “low” concentrations that are not high enough to achieve MIC at the administration site

• EXAMPLE: adding more drug to manufactured 0.3% solution to bring it to a 1.4% concentration
Topical Eye Drops: Choice of Diluent Vehicle

• Choice of BSS, SWFI, NS, AT (artificial tears)

• **Artificial Tears (AT)** have several advantages:
  • Artificial tears vehicle is already manufactured to be suitable for the eye
  • Viscosity prolongs contact time to corneal tissues
  • Contains preservatives that help extends shelf life (but not beyond chemical/physical drug stability)
    • Most BUDs will be limited by drug stability
    • Shelf life extensions can be up to 3 and 6 months
  • Also comes with a “free” bottle (carefully remove the tip with bag or sterile gloves)

Topical Eye Drops: Voriconazole 10 mg/mL (1%)

1. Reconstitute a 200 mg vial of voriconazole powder with 19 mL of preservative-free sterile water for injection = 10 mg/mL (1%) = final concentration

2. Transfer the solution into an sterile empty eye dropper using a 5-micron FILTER NEEDLE.

3. Stability: 30 days FR; 30 days RT
Topical Eye Drops:
Cefazolin 50 mg/mL (5%) FORTIFIED

1. Reconstitute a 1 Gram vial of cefazolin powder with 9.2 mL of artificial tears = 100 mg/mL (10%)

2. Transfer 5 mL of solution from step 1 into a sterile empty eye dropper using a 5-micron FILTER NEEDLE.

3. Add 5 mL of additional artificial tears to the dropper for a final concentration of 50 mg/mL (5%)

4. Stability: 14 days FR; 72 hours RT

Yogesh 2011, McElhiney 2013, Rojanarata 2010
Topical Eye Drops:
Ceftazidime 50 mg/mL (5%) FORTIFIED

1. Reconstitute a 1 Gram vial of ceftazidime powder with 9.2 mL of artificial tears = 100 mg/mL (10%)
2. Transfer 5 mL of solution from step 1 into a sterile empty eye dropper using a 5-micron FILTER NEEDLE.
3. Add 5 mL of additional artificial tears to the dropper for a final concentration of 50 mg/mL (5%)
4. Stability: 14 days FR; 24 hours RT

Topical Eye Drops:
Gentamicin 14 mg/mL (1.4%) FORTIFIED

1. Start with commercially available 5 mL bottle of Gentamicin 0.3% (3 mg/mL) ophthalmic solution (15 mg in bottle).

2. Using gentamicin injection 40 mg/mL, add 2.13 mL (85.2 mg) = ~100 mg/7.13 mL = 14 mg/mL.

3. Stability: 14 days FR; 48 hours RT

Topical Eye Drops:
Tobramycin 14 mg/mL (1.4%) FORTIFIED

1. Start with commercially available 5 mL bottle of Tobramycin 0.3% (3 mg/mL) ophthalmic solution (15 mg in bottle).

2. Using tobramycin injection 40 mg/mL, add 2.13 mL (85.2 mg) = ~100 mg/7.13 mL = 14 mg/mL.

3. Stability: 14 days FR; 48 hours RT
Topical Eye Drops:
Vancomycin 25 mg/mL (2.5%) FORTIFIED

1. Reconstitute a 500 mg vial of vancomycin with 10 mL NS or artificial tears = 50 mg/mL
2. Withdraw the entire contents of the vial and transfer to a sterile empty vial (20 mL capacity) using a 5-micron FILTER NEEDLE.
3. Add 10 mL of NS or artificial tears = 25 mg/mL
4. Stability = 14 days FR, 14 days RT

*NOTE: If mixed in SWFI, pH is 2.5 – 4.5 (too low)*

Preferred diluent vehicle is NS or artificial tears

Topical Eye Drops: Appropriate Bottle Labelling

- **Drug Name**: Vancomycin Fortified Eye Drops
- **Drug Strength**: 2.5% (25 mg/mL)
- **Administration Route**: For Ophthalmic Use Only
- **Preparation Date**: mm/dd/yyyy
- **Expiration Date/BUD**: mm/dd/yyyy
- **Storage Directions**: (fridge or room temp)
- **Compounded By**: (name of pharmacy + compounder)
- **Compounded Product Lot Number**
- **Patient labelling on outer package per regulations**

USP 797 (labeling and dispensing compounded sterile products), FDA, State and Federal Regulations (may vary), International Regulations (may vary)
Topical Eye Drops: Appropriate Patient Labelling

- Patient labelling on outer package per regulations

Date: 2018-09-23  
RX# OUTP-2018-09-23-1-MF  
**PATIENT:** Jane Doe

**PRESCRIBER:** John Smith, MD  
Saint Agnes Medical Center  
1303 E Herndon Ave, Fresno, CA 93720  
Phone: 559-450-3132

**Vancomycin Fortified Eye Drops 25 mg/mL (2.5% solution)**  
DISPENSE: total volume = 15 mL (2 bottles = 30 mL)  
Compounded by Saint Agnes Medical Center Pharmacy

**DIRECTIONS FOR USE:** instill 1 drop every hour into LEFT EYE, separate from other eye drops by 10 minutes.  
**REFRIGERATE:** discard after 14 days

**CAUTIONS:** stop using and contact your ophthalmologist immediately in the event of worsening irritation, soreness, burning, or light sensitivity occurs.

NABP Task Force on Uniform Prescription Labeling Requirements, State and Federal Regulations (may vary), International Regulations (may vary)  
# Appendix 8: Ophthalmic Preparations

**Technique Notes:** Compound using aseptic technique. Do NOT inject needle through the dropper tips, this will alter the drop size. Easily remove dropper tips by placing the bottles inside a clean Ziploc bag. This provides an easy grip through the plastic (with friction) to push sideways and pop off the tip which will then stay in the bag. Dropper bottles are able to accommodate more than what is printed on the label. Always use sterile dropper bottles. **Note:** 0.1% = 1 mg/mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Frequency</th>
<th>Route</th>
<th>Volume</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amikacin Fortified</strong></td>
<td>FR 14 d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RT 24 hr</td>
<td>14 d (FR)</td>
<td>NS(PF)</td>
</tr>
<tr>
<td><strong>2.5% = 25 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td>1. Amikacin is supplied in solution as 250 mg/mL&lt;br&gt;2. Withdraw 1 mL Amikacin (250 mg/mL) and add to 9 mL NS(PF) = 250 mg/10 mL&lt;br&gt;3. Add the 25 mg/mL dilution to an available size sterile empty eye dropper bottle&lt;br&gt;4. Storage: REFRIGERATE</td>
</tr>
<tr>
<td><strong>10 mL in eye dropper bottle</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Amikacin Fortified</strong></td>
<td>FR 14 d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RT 24 hr</td>
<td>14 d (FR)</td>
<td>NS(PF)</td>
</tr>
<tr>
<td><strong>5% = 50 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td>1. Amikacin is supplied in solution as 250 mg/mL&lt;br&gt;2. Withdraw 2 mL Amikacin (250 mg/mL) and add to 8 mL NS(PF) = 500 mg/10 mL&lt;br&gt;3. Add the 50 mg/mL dilution to an available size sterile empty eye dropper bottle&lt;br&gt;4. Storage: REFRIGERATE</td>
</tr>
<tr>
<td><strong>10 mL in eye dropper bottle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>FR 7 d</td>
<td>RT 48 hr</td>
<td>7 d (FR)</td>
<td>SWFI(PF)</td>
</tr>
<tr>
<td>(conventional formulation)</td>
<td></td>
<td></td>
<td></td>
<td>1. Dilute a 50 mg Amphotericin B vial (stored in fridge) w/ 10 mL SWFI(PF) = 5 mg/mL&lt;br&gt;2. Withdraw 7.5 mL of 5 mg/mL; inject into a 30 mL syringe using a <em>FILTER NEEDLE</em>&lt;br&gt;3. Add 17.5 mL of SWFI(PF) into the 30 mL syringe, final concentration = 37.5 mg/25 mL&lt;br&gt;4. Add the 1.5 mg/mL dilution into an available sterile empty dropper bottle&lt;br&gt;5. Storage: REFRIGERATE, protect from light (use amber or non-transparent plastics). <strong>Do NOT use Ambisome® Liposomal; Amphotericin B vials are stored in the refrigerator.</strong></td>
</tr>
<tr>
<td><strong>0.15% = 1.5 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20 mL in eye dropper bottle</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>FR 7 d</td>
<td>RT 48 hr</td>
<td>7 d (FR)</td>
<td>SWFI(PF)</td>
</tr>
<tr>
<td>(conventional formulation)</td>
<td></td>
<td></td>
<td></td>
<td>1. Dilute a 50 mg Amphotericin B vial (stored in fridge) w/ 10 mL SWFI(PF) = 5 mg/mL&lt;br&gt;2. Withdraw 10 mL of 5 mg/mL; inject into a sterile dropper bottle w/ <em>FILTER NEEDLE</em>&lt;br&gt;3. Storage: REFRIGERATE, protect from light (use amber or non-transparent plastics). <strong>Do NOT use Ambisome® Liposomal; Amphotericin B vials are stored in the refrigerator.</strong></td>
</tr>
<tr>
<td><strong>0.5% = 5 mg/mL</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>10 mL in eye dropper bottle</strong></td>
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<td></td>
</tr>
</tbody>
</table>
### Review Everything: Standardize, Simplify, Educate

<table>
<thead>
<tr>
<th>Compound</th>
<th>Strength</th>
<th>Dilution</th>
<th>Storage</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin Fortified Eye</td>
<td>5% = 50 mg/mL</td>
<td>16 mL in eye dropper bottle</td>
<td>FR 14 d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RT 72 hr&lt;br&gt;14 d (FR) SWFI(PF) &amp; Artificial Tears&lt;br&gt;1. Dilute a 1 gram Cefazolin vial w/ 5 mL SWFI(PF) = 200 mg/mL&lt;br&gt;2. Withdraw 12 mL of Artificial Tears into a 20 mL syringe and discard the remaining solution, save the bottle to hold the final concentration.&lt;br&gt;3. Withdraw 4 mL of Cefazolin 200 mg/mL and inject into the 20 mL syringe with the 12 mL Artificial Tears using a <em>FILTER NEEDLE</em> = 800 mg/16 mL = 50 mg/mL = 5%&lt;br&gt;4. Add the 50 mg/mL dilution back into the original Artificial Tears bottle.&lt;br&gt;5. Storage: REFRIGERATE</td>
</tr>
<tr>
<td>Cefazidime Fortified</td>
<td>5% = 50 mg/mL</td>
<td>20 mL in eye dropper bottle</td>
<td>FR 7 d</td>
<td>RT 24 hr&lt;br&gt;7 d (FR) NS(PF) &lt;br&gt;1. Dilute a 1 gram Cefazidime vial w/ NS or BSS to make a 100 mg/mL concentration (each manufacturer's product has a different powder volume displacement, check the package insert for the appropriate amount of diluent to add to each vial)&lt;br&gt;2. Withdraw 10 mL of 100 mg/mL; inject into a 20 mL syringe using a <em>FILTER NEEDLE</em>&lt;br&gt;3. Add 10 mL of NS or BSS into the 20 mL syringe, final concentration = 50 mg/mL = 5%&lt;br&gt;4. Add the 50 mg/mL dilution into an available size sterile empty eye dropper bottle.&lt;br&gt;5. Storage: REFRIGERATE</td>
</tr>
<tr>
<td>Gentamicin Fortified</td>
<td>1.4% = 14 mg/mL &lt;br&gt;7.13 mL in eye 10 mL bottle</td>
<td>FR 14 d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RT 48 hr</td>
<td>14 d (FR) Gent. Solution + drug&lt;br&gt;1. Start with the commercially available 5 mL Gentamicin 0.3% (3 mg/mL) solution.&lt;br&gt;2. Add 2.13 mL of Gentamicin 80 mg/2 mL injection = 100 mg/7.13 mL = 14 mg/mL&lt;br&gt;3. Storage: REFRIGERATE</td>
</tr>
<tr>
<td>Gentamicin Fortified</td>
<td>1.5% = 15 mg/mL &lt;br&gt;7.4 mL in eye 10 mL bottle</td>
<td>FR 14 d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RT 48 hr</td>
<td>14 d (FR) Gent. Solution + drug&lt;br&gt;1. Start with the commercially available 5 mL Gentamicin 0.3% (3 mg/mL) solution.&lt;br&gt;2. Add 2.4 mL of Gentamicin 80 mg/2 mL injection = 111 mg/7.4 mL = 15 mg/mL&lt;br&gt;3. Storage: REFRIGERATE</td>
</tr>
<tr>
<td>Treatment</td>
<td>FR</td>
<td>RT</td>
<td>Duration</td>
<td>Administration</td>
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<td>---------------------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Tobramycin Fortified</td>
<td>14</td>
<td>48</td>
<td>14 days</td>
<td>Tobra. Solution + drug</td>
</tr>
<tr>
<td>1.4% = 14 mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.13 mL in 10 mL bottle</td>
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<td></td>
</tr>
<tr>
<td>Tobramycin Fortified</td>
<td>14</td>
<td>48</td>
<td>14 days</td>
<td>Tobra. Solution + drug</td>
</tr>
<tr>
<td>1.5% = 15 mg/mL</td>
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<td></td>
<td></td>
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<tr>
<td>7.4 mL in 10 mL bottle</td>
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<tr>
<td>Vancomycin Fortified</td>
<td>14</td>
<td>7</td>
<td>14 days</td>
<td>Artificial Tears (or) NS</td>
</tr>
<tr>
<td>2.5% = 25 mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mL in eye dropper bottle</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin Fortified</td>
<td>14</td>
<td>7</td>
<td>14 days</td>
<td>Artificial Tears (or) NS</td>
</tr>
<tr>
<td>5% = 50 mg/mL</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20 mL in eye dropper bottle</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole 1%</td>
<td>30</td>
<td>30</td>
<td>14 days</td>
<td>SWFI(PF)</td>
</tr>
<tr>
<td>1% = 10 mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mL in eye dropper bottle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole 2%</td>
<td>30</td>
<td>30</td>
<td>14 days</td>
<td>SWFI(PF)</td>
</tr>
<tr>
<td>2% = 20 mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mL in eye dropper bottle</td>
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</tbody>
</table>

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Objective 3

• Review the compounding staff's education and processes to increase patient safety.
Compounding Ophthalmic Preparations

1. Eye Anatomy
   - Injection sites of Ophthalmic Preparations
   - Requirements for Ophthalmic Preparations

2. Master Formula Requirements
   - Research and References to Use
   - Important Factors to Consider
   - Writing a Master Formula

3. Review Compounding Staff’s Education
   - Example Drug Errors and Avoidance
   - Education for the Staff and the Patient
Compounding Program Elements

- Employee Education
- Employee Safety
- Quality Assurance
- Compounding Process
- Regulatory Compliance

Patient Safety
Hazardous Drug Compounding Program Elements
Understanding How Drug Errors Occur

• Lack of knowledge on the products
• Failure to recognize an incorrect order
• Incorrectly written compounding formula
• Compounding formula was not understood
• Wrong solutions were used for dilution
• Parts of formula were missed (critical steps)
• No formula available, compounder calculated (incorrectly)
• Compounder was distracted, forgot the required filter needle
• Final preparation not double checked (preventable error?)
Drug Error: Amphotericin B

• EVENT: Amphotericin B (conventional) 0.5% in BSS
• How did this happen?
• INCOMPATIBLE SOLUTION USED TO DILUTE DRUG
• RESULT: drug incompatibility
• Amphotericin B (conventional or liposomal) is only compatible in D5W or SWFI, and not NS or BSS
Drug Error: Amphotericin B

• EVENT: Amphotericin B (liposomal) 0.5% in SWFI for intravitreal injection

• How did this happen?

• WRONG FORMULATION USED

• RESULT: drug not effective, unpredictable results when given intravitreal

• Needed to use the conventional formulation and not the liposomal
Drug Error: Amphotericin B

- EVENT: Amphotericin B (conventional) 0.5% in SWFI for intravitreal injection, made as 500 mcg/0.1 mL instead of the required 5 mcg/0.1 mL
- WRONG CONCENTRATION MADE
- How did this happen?
- RESULT: severe inflammation, lens opacity, vision reduction

**Drug Error: Gentamicin**

- **EVENT:** Gentamicin 14% eye drops were ordered (140 mg/mL)
- **How did this happen?**
- **WRONG DOSE ORDERED, WRONG CONCENTRATION MADE**
- **RESULT:** missing decimal, should be 1.4% (14 mg/mL)
- **In checking the actual physician order, is the actual concentration, dose, injection site, frequency correct?**
- **Sometimes internal medicine or emergency room physicians consult ophthalmologists and/or eye surgeons and can transcribe the consultant’s orders incorrectly.**
Drug Error: Cefazolin

- EVENT: Cefazolin 100 mg/0.1 mL made for intravitreal injection
- How did this happen?
  - **WRONG DOSE ORDERED:** 100 mg is for subconjunctival injection
  - **RESULT:** dose is 2.25 mg/0.1 mL for intravitreal injection
- In checking the actual physician order, is the actual concentration, dose, injection site, and frequency correct?
- Sometimes internal medicine or emergency room physicians consult ophthalmologists and/or eye surgeons and can transcribe the consultant’s orders incorrectly.

Reference

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### Comparison of Doses & Administration Routes

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Topical (1% = 10 mg/mL)</th>
<th>Subconjunctival (per 0.5 mL)</th>
<th>Intravitreal (per 0.1 mL)</th>
<th>Intravenous</th>
<th>Infusion (mcg/mL)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>20 – 50 mg/mL</td>
<td>25 – 125 mg</td>
<td>125 – 400 mcg</td>
<td>15 mg/kg/day in 2 divided doses</td>
<td>8 – 10</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>1 – 5 mg/mL</td>
<td>--</td>
<td>5 – 10 mcg</td>
<td>--</td>
<td>10 – 20</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>--</td>
<td>100 mg</td>
<td>100 mcg</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>4 – 6 mg/mL</td>
<td>100 mg</td>
<td>2 mg</td>
<td>15 – 30 Gm in 4 – 6 divided doses</td>
<td>--</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>50 mg/mL</td>
<td>100 mg</td>
<td>2 – 2.25 mg</td>
<td>1 – 6 Gm daily in 3 – 4 divided doses</td>
<td>--</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>50 mg/mL</td>
<td>100 – 200 mg</td>
<td>2 – 2.25 mg</td>
<td>2 – 6 Gm daily in 2 – 3 divided doses</td>
<td>40 – 50</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3 mg/mL</td>
<td>--</td>
<td>100 mcg</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

<sup>a</sup>Infusion: maximum prophylactic non-toxic doses, used per-operatively.

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Peyman GA, Lad EM, Moshfeghi DM. Intravitreal Injection of Therapeutic Agents. Retina 2009; 29: 875-912
## Comparison of Doses & Administration Routes

| Antibiotic       | Topical (1% = 10 mg/mL) | Subconjunctival (per 0.5 mL) | Intravitreal (per 0.1 mL) | Intravenous                                      | Infusion (mcg/mL)
|------------------|-------------------------|-----------------------------|---------------------------|-------------------------------------------------|------------------
| Clindamycin      | 50 mg/mL                | 15 – 50 mg                  | 1 mg                      | 0.6 – 3.6 Gm daily in 3 – 4 divided doses        | 9                |
| Gentamicin       | 10 – 20 mg/mL           | 10 – 20 mg                  | 80 – 200 mcg              | 3 – 5 mg/kg/day in 2 – 3 divided doses          | 8                |
| Imipenem/Cilastatin | 5 mg/mL              | --                          | 50 – 100 mcg              | 2 Gm daily in 3 – 4 divided doses               | 16               |
| Moxifloxacin     | 5 mg/mL                 | --                          | 50 – 200 mcg              | --                                              | --               |
| Natamycin        | 5% suspension           | Not indicated               | Not indicated             | Extremely toxic                                 | --               |
| Penicillin G     | 100,000 – 200,000 U/mL  | 0.5 – 1 M units             | --                        | 2 – 18 million Units daily in 4 – 6 divided doses | 80               |

*aInfusion: maximum prophylactic non-toxic doses, used per-operatively.*


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## Comparison of Doses & Administration Routes

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<th>Subconjunctival (per 0.5 mL)</th>
<th>Intravitreal (per 0.1 mL)</th>
<th>Intravenous</th>
<th>Infusion (mcg/mL)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>6 – 20 mg/mL</td>
<td>100 mg</td>
<td>225 mcg</td>
<td>6 – 12 Gm every 4 – 6 hours</td>
<td>--</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>4 – 6 mg/mL</td>
<td>100 mg</td>
<td>3 mg</td>
<td>200 – 300 mg/kg daily in 4 – 6 divided doses</td>
<td>--</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>10 – 20 mg/mL</td>
<td>10 – 20 mg</td>
<td>100 – 200 mcg</td>
<td>3 – 5 mg/kg daily in 2 – 3 divided doses</td>
<td>10</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>25 – 50 mg/mL</td>
<td>25 mg</td>
<td>1 mg</td>
<td>2 Gm daily in 2 doses</td>
<td>30 – 200</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>10 mg/mL</td>
<td>10 mg (not used)</td>
<td>50 – 100 mcg</td>
<td>6 mg/kg IV every 12 hours (24 hours), then 4 mg/kg x 12 hr or 200 mg/day divided twice daily</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

<sup>a</sup>Infusion: maximum prophylactic non-toxic doses, used per-operatively.

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Peyman GA, Lad EM, Moshfeghi DM. Intravitreal Injection of Therapeutic Agents. Retina 2009; 29: 875-912
Drug Error: Vancomycin

- **EVENT:** Vancomycin 50 mg/mL topical drops made with SWFI
- **How did this happen?**
- **WRONG SOLUTION USED (should use BSS, NS, or AT)**
- **RESULT:** corneal toxicity, pain, irritation, inflammation

- Needed to use BSS, NS, or AT (artificial tears) - preferred
  - SWFI + Vancomycin 50 mg/mL pH = 2.5 – 4.5
  - BSS + Vancomycin 50 mg/mL pH = 5.4 – 5.6, 7.1
  - NS + Vancomycin 50 mg/mL pH = 5.4
  - D5W + Vancomycin 50 mg/mL pH = 4.2
  - AT + Vancomycin 50 mg/mL pH = 6.8 – 7.6

Employee Education: Compounding Ophthalmics

- Provide employee education on compounding ophthalmic drugs.
- Employees must demonstrate understanding before compounding.
- Recommend having the compounding process carried out by advanced level personnel that can compound these on a regular basis (if batching) and avoid errors due to lack of experience.
- Management should have confidence that staff can follow the complicated compounding formulas that sometimes require multiple serial dilution steps, filtration, and careful technique.
- Setup independent verification for each of these preparations.
Compounding: ISMP Safety Best Practices

- At a minimum, perform an **independent verification** for all:
  - High-alert medications (including chemotherapy and parenteral nutrition)
  - Pediatric/Neonatal preparations
  - Pharmacy-prepared source/bulk containers
  - Products administered via high-risk routes of administration (e.g., intrathecal, epidural, **intraocular**), and
  - Other compounded sterile preparations that the organization believes are high-risk.

- **Independent verification**: ensuring correct ingredients (medications, diluents), and correct volumes added at each step prior to addition to the final container.
Question: Can you convert % to mg/mL?

You receive an order for vancomycin 2.5% ophthalmic drops, what is this in mg/mL?

a. 25 mg/mL
b. 2.5 mg/mL
c. 0.25 mg/mL
d. 0.025 mg/mL
You receive an order for vancomycin 2.5% ophthalmic drops, what is this in mg/mL?

a. 25 mg/mL
b. 2.5 mg/mL
c. 0.25 mg/mL
d. 0.025 mg/mL
Employee Education: Calculations & Conversions

- % Concentration ↔ mg/mL
- Grams (Gm) ↔ Milligrams (mg) ↔ Micrograms (mcg) (μg)
- Basic math, ratios, fractions, units of measure
- Math involved in dilutions and serial dilutions

0.1% = 1 mg/mL
1% = 10 mg/mL
You need to compound bupivacaine 0.25% with **epinephrine 1:200,000** for an eye procedure during a drug shortage. You have bupivacaine and NS. How much **epinephrine 1:200,000** is needed to make a 30 mL syringe?
Can you convert ratios to mg/mL?

You need to compound bupivacaine 0.25% with epinephrine 1:200,000 for an eye procedure during a drug shortage. You have bupivacaine and NS. How much epinephrine 1:200,000 is needed to make a 30 mL syringe?

1:100,000 = 0.01 mg/mL
1:200,000 = 0.005 mg/mL

You need 0.005 mg/mL x 30 mL = 0.15 mg
You have received an order for fortified gentamicin 1.4% eye drops for a patient with endophthalmitis. Aside from confirming employee education for compounding, who else may need education? *(select all that apply)*

a. Physician  
b. Clinic nurse  
c. Patient  
d. Patient’s caregiver
You have received an order for fortified gentamicin 1.4% eye drops for a patient with endophthalmitis. Aside from confirming employee education for compounding, who else may need education? *(select all that apply)*

a. Physician  ➔ *research and dosing assistance, writing order*
b. Clinic nurse ➔ *correct administration, storage*
c. Patient ➔ *correct administration, storage*
d. Patient’s caregiver ➔ *correct administration, storage*
Employee Education: The Clinical Pharmacist

• Is the ophthalmic prescription correct?
• What resources are there to learn about the doses?
• Do I have the information to compound this correctly?
• Will you be able to counsel the patient correctly on the compounded ophthalmic products?
  • How often to administer
  • Wash hands before administration
  • Administration technique
  • Storage of eye drops
  • Expiration of eye drops
Patient Education: Topical Ophthalmics

- Patient counseling on how to use the preparations is important.
- Need to know how to use topical eye drops, spacing apart (5 – 10 min), how to put into eye.
- Storage and expiration of eye drops.

How to Use Eye Drops Properly

1. Wash your hands thoroughly with soap and water.
2. Check the dropper tip to make sure that it is not chipped or cracked.
3. Avoid touching the dropper tip against your eye or anything else — eyedrops and droppers must be kept clean.
4. While tilting your head back, pull down the lower lid of your eye with your index finger to form a pocket.
5. Hold the dropper (tip down) with the other hand, as close to the eye as possible without touching it.
6. Breeze the remaining fingers of that hand against your face.
7. While looking up, gently squeeze the dropper so that a single drop falls into the pocket made by the lower eyelid. Remove your index finger from the lower eyelid.
Patient Education: Administering Eye Drops

1. Wash hands.
2. With one hand, gently pull lower eyelid down.
3. If dropper is separate, squeeze rubber bulb once while dropper is in bottle to bring liquid into dropper.
4. Holding dropper above eye, drop medicine inside lower lid while looking up; do not touch dropper to eye or fingers.
5. Release lower lid. Try to keep eye open and not blink for at least 30 seconds.
6. If dropper is separate, replace on bottle and tighten cap.

Directions

Patient Education: Administering Eye Drops

1. If dropper is separate, always hold it with the tip down.
2. Never touch dropper to any surface, and never rinse the dropper.
3. When dropper is at top of bottle, avoid contaminating cap when removed.
4. When dropper is a permanent fixture on the bottle (i.e., when supplied by a pharmaceutical manufacturer to the pharmacist), the same rules apply to avoid contamination.
5. Never use eye drops that have changed color.
6. If you are using more than one kind of drop at the same time, wait several minutes before using other drops.
7. After instillation of drops, do not close eyes tightly and try not to blink more often than usual, as this removes the medicine from the place on the eye where it will be effective.

Warnings

Question: Would you proceed to fill this order?

Tobramycin 14% fortified ophthalmic solution
Instill 1 drop every 1 hour x 3 days
Question: Would you proceed to fill this order?

Tobramycin 14% fortified ophthalmic solution
Instill 1 drop every 1 hour x 3 days

NO: the concentration should be 14 mg/mL or 1.4%, and not 14%
Vancomycin 5% fortified ophthalmic solution
Instill 1 drop every 2 hours x 7 days
Question: Would you proceed to fill this order?

Vancomycin 5% fortified ophthalmic solution
Instill 1 drop every 2 hours x 7 days

YES: correct concentration and dosing
Ceftazidime 2.25 mg/0.1 mL intravitreal injection
Injected by physician during surgery
Ceftazidime 2.25 mg/0.1 mL intravitreal injection
Injected by physician during surgery

YES: correct concentration and dosing
Question: Would you proceed to fill this order?

Voriconazole 50 mg/0.1 mL intravitreal injection
Injected by physician during surgery
Question: Would you proceed to fill this order?

Voriconazole 50 mg/0.1 mL intravitreal injection
Injected by physician during surgery

NO: concentration needs to be 50 mcg/0.1 mL for the intravitreal order
Question: Would you proceed to fill this order?

Amphotericin B 5 mcg/0.1 mL intravitreal inj. Injected by physician during surgery
Amphotericin B 5 mcg/0.1 mL intravitreal inj.
Injected by physician during surgery

YES: correct concentration and dosing
Question: What formulation do you use?

Amphotericin B 5 mcg/0.1 mL intravitreal inj. Injected by physician during surgery
Amphotericin B 5 mcg/0.1 mL intravitreal inj. Injected by physician during surgery

Use the conventional formulation (do not use liposomal)
Question: Would you accept this?

Amphotericin B 5 mcg/0.1 mL intravitreal inj.
For injection by physician during surgery
You are inspecting the syringe prepared by the compounding technician, do you accept it?
Question: Would you accept this?

Amphotericin B 5 mcg/0.1 mL intravitreal inj. For injection by physician during surgery

You are inspecting the syringe prepared by the compounding technician, do you accept it?

NO: solution is too yellow, and likely compounded incorrectly.

Conclusion

• **Ophthalmic** preparations require extra attention to ensure accuracy in compounding *(for patient safety)*

• Review master formula requirements to ensure all regulatory requirements are met *(for patient safety)*

• Standardize your compounded products *(for patient safety)*

• Practice making these unique preparations in employee education

• Organize references (and save everything you read)

• Share information and educate others

• **Become the expert in your pharmacy!!!**
References: Books & Guidelines

- USP-NF General Chapter <797> [USP39/NF34]
- Trissel’s Stability of Compounded Formulations
- Trissel’s Handbook on Injectable Drugs
- Trissel's Clinical Pharmaceutics Database
- King Guide to Parenteral Admixtures
- Extended Stability of Parenteral Drugs (Bing)
- American Journal of Hospital Pharmacy (AJHP)
- NIOSH List of Hazardous Drugs 2016
- Institute for Safe Medication Practices (ISMP)
- ASHP Guidelines on Compounding Sterile Preparations
- ASHP Guidelines on Quality Assurance for Pharmacy Sterile Products
- ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products


• Flynn HW, Relhan N. Recognition, Treatment and Prevention of Endophthalmitis. University of Miami School of Medicine. 2016
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• ISMP Targeted Medication Safety Best Practices Checklist 2018-2019
• McElhiney, Linda F. Compounding Guide for Ophthalmic Preparations. APhA, 2013. (out of print)

• NABP Task Force on Uniform Prescription Labeling Requirements


• Peyman GA, Lad EM, Moshfeghi DM. Intravitreal Injection of Therapeutic Agents. Retina 2009; 29: 875-912
References


Questions?

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