NEW CHANGES COMING FOR ANTIFIBROTIC/ANTIMETABOLITE MEDICATIONS

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A review of their use in glaucoma surgery and considerations around ophthalmic compounding.

Antifibrotics and antimetabolites, including 5-fluorouracil (5-FU) and mitomycin c (MMC), have been used for decades to improve ophthalmic surgical outcomes, including trabeculectomy and newer minimally invasive subconjunctival drainage devices. A review of the usage and safety of these agents is merited, especially in light of updated and new USP (formerly United States Pharmacopeia) guidelines for compounded and hazardous drugs.

Use of MITOMYCIN C and 5-FU

MMC has been successful in ophthalmic surgery as it reduces collagen synthesis and proliferation.[1-3] MMC is cytotoxic and affects nearly all profibrotic processes of conjunctival fibroblasts and endothelial cells.[4,5] Similarly, the role of 5-FU is to reduce fibroblast proliferation and subsequent scarring, and it is often used off label in ocular and periorbital surgeries.[6] The FDA-approved MMC product, mitomycin solution 0.2 mg/vial (Mitosol, Mobius Therapeutics, LLC), is commercially available in a single-use formulation used both on and off label for several ophthalmic surgeries, including topical application to the surgical site of glaucoma filtration surgery.[7]

Perioperative administration of MMC is evolving with a shift from the traditional sponge application to a subconjunctival injection allowing for a more precise dosing and controlled administration. There are no universal concentrations for injected MMC that have emerged yet as a "gold standard" during subconjunctival microinvasive glaucoma surgery (MIGS). MMC in doses ranging from 0.1 to 0.4 mg/ml have been used with subconjunctival drainage procedures such as trabeculectomy and XEN Gel Stent implantation (Allergan).

Because MMC sponge application or the FDA-approved strengths of MMC may not be clinically appropriate, ophthalmologists are often unable to use name brand or generic versions of MMC during certain subconjunctival filtration surgeries. The ophthalmic use of 5-FU is also limited by the same constraints because there is no FDA-approved product for topical and subconjunctival administration. In such situations, ophthalmologists seek out compounded versions of MMC and 5-FU through their own pharmacy or elsewhere. The concentrations of compounded MMC that glaucoma surgeons receive are typically between 0.2 and 0.4 mg/ml with higher doses customized to address higher risk of scarring such as previous surgery, young age, and race/ethnicity.[8]

REGULATIONS OF ANTIFIBROTICS

The FDA expects physicians to prescribe and administer FDA-approved drugs whenever they are commercially available because such drugs are subject to their rigorous premarket review for safety, effectiveness, and quality. In addition, these drugs are also manufactured by a facility that is subject to the FDA's stringent current good manufacturing practices (cGMP). However, the FDA recognizes that it may be necessary to modify a commercially available drug product in order to provide a clinically meaningful difference to an individual patient.

The FDA requires pharmacies that are compounding drugs to follow standards set by Chapter <797> of the USP to reduce the potential for infection and harm that can be caused by compounding sterile pharmaceutical products. Special emphasis is placed on minimizing risk of contamination and adulteration of medicines whilst compounding sterile preparations.[9] Compounded MMC and 5-FU must be compounded to USP <797> standards; they are regulated under state pharmacy and FDA boards.

In addition to sterile compounding regulations, MMC and 5-FU are classified as hazardous drugs (chemotherapeutic agents) by the National Institute of Occupational Safety and Health (NIOSH).[10-12] NIOSH also notes that these drugs "represent an occupational hazard to health care workers and should always be handled with use of recommended engineering controls and personal protective equipment regardless of their formulation."[12] Similar warnings are issued in regards to risks exposure to MMC and 5-FU present to pregnant health care providers.[12,13]

A newer compounding standard, USP <800> "Hazardous Drug Handling in the Health Care Setting," is approved with an expected

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>>To read the original paper, please visit bit.ly/MMCinCurrentTrendsOphthal

compliance beginning on December 1, 2019. USP <800> is primarily focused on protecting health care workers, patients, and the general public who have access to facilities where hazardous drugs are stored, prepared, and administered.[13]

COMPLIANCE

The Centers for Medicare and Medicaid Services require facilities receiving reimbursement to ensure compliance with USP standards for products used on patients and billed to the Centers for Medicare and Medicaid Services.

Whereas, FDA-registered outsource manufacturers operating under Section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act are required to follow the more stringent FDA cGMP compounding regulations. Compounding pharmacies that handle MMC and 5-FU must adhere to USP <797> for patient safety and must adhere to USP <800> for health care provider safety. FDA-registered outsourcing facilities must comply with an even more stringent set of standards. Defined within USP <800> are requirements for the use of specially designed personal protective equipment (e.g. two pairs of chemotherapy gloves, which are rated ASTM D6978), use of special engineering controls (e.g. biological safety cabinets and closed-system drug transfer devices for compounding and administration of hazardous drugs), and facility requirements for the safe storage, compounding, and disposal of sterile and nonsterile anti-neoplastic hazardous drugs.[14]

SELECTING A COMPOUNDING PHARMACY

The introduction of minimally invasive subconjunctival procedures will potentially increase the use of MMC and 5-FU. Thus, there is a need for surgeons to be aware of the safety, efficacy, and safe handling of these drugs especially in light of updated and new USP regulations.

>>Questions to Ask When Selecting a Compounding Pharmacy

When vetting a compounding pharmacy issuing 5-fluorouracil (5-FU) and mitomycin c (MMC), physicians should specifically ask the pharmacist in charge the following questions:

1. Is the facility operating under Section 503A or Section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act?[1-4] A physician should be wary of a facility that claims it is regulated by the FDA, or claims to be operating under Section 503A of the FD&C Act, yet is obviously not engaged in traditional pharmacy compounding, e.g., it is not universally asking for prescriptions for individually identified patients prior to dispensing drugs or is manufacturing in large quantities.
2. Will the facility be compounding the MMC and 5-FU from FDA-approved drugs rather than from bulk drug substances?
3. Will the facility conduct testing to confirm both sterility and stability of the product for the assigned beyond-use date?
4. Is the facility licensed by a state authority (for facilities operating under Section 503A of the FD&C Act) or registered with the FDA (for facilities operating as outsourcing facilities under Section 503B of the FD&C Act)? This can be referenced by visiting the FDA's Registered Outsourcing Facilities website: **www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm**
5. Does the facility comply with chapter <797> of the USP (for facilities operating under Section 503A of the FD&C Act) or with the FDA's cGMP regulations (for facilities operating as outsourcing facilities under Section 503B of the FD&C Act)?
6. Physicians should specifically ask whether in the last 5 years the FDA has issued the facility a Form 483 (describes violations of the FD&C Act found during an FDA inspection) and/or a warning letter.[5]
7. Has a state regulatory authority within the last 5 years issued the facility and/or its owners an inspection report, regulatory letter, or Cease and Desist order?
8. Has the facility had to recall compounded products within the last 5 years?

Document the facility's answers to the questions discussed previously (along with your own assessment of the facility). Include any documentation that can be procured (such as Form 483s and warning letters) that show whether the compounding facility is adherent to compounding standards (USP <797> for 503A facilities and current good manufacturing practices for 503B outsourcing facilities) and USP <800>.

The business agreement between the physician and the pharmacist should require:

- The facility to provide the physician with real-time notification of any adverse events or recalls associated with compounded drug products.
- The facility to promptly share any communications between the facility and FDA and/or state regulators, including inspection reports and warning letters that relate to the safety, efficacy, or quality of compounded drugs.
- The facility's commitment to complying with all applicable federal and state requirements, along with all relevant USP chapters, including chapter <800>.

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2. US Food & Drug Administration. Research C for DE and compounded drug products that are essentially copies of a commercially available drug product under section 503a of the federal food, drug, and cosmetic act guidance for industry. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/compounded-drug-products-are-essentially-copies-approved-drug-products-under-section-503b-federal; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryregulatoryinformation/guidances/UCM510153.pdf. Published January 2018. Accessed April 27, 2019.
3. US Food & Drug Administration. Research C for DE and pharmacy compounding of human drug products under section 503a of the federal food, drug, and cosmetic act guidance. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacy-compounding-human-drug-products-under-section-503a-federal-food-drug-and-cosmetic-act; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM469119.pdf. Published June 2016. Accessed April 27, 2019.
4. US Food & Drug Administration. Facility definition under section 503b of the federal Food, Drug, and Cosmetic Act: guidance for industry. Available at: https://www.fda.gov/downloads/drugs/guidances/UCM496288.pdf. Published May 2018. Accessed June 24, 2018.
5. US Food & Drug Administration. FDA form 483 frequently asked questions. Available at: https://www.fda.gov/iceci/inspections/ucm256377.htm. Accessed October 4, 2019.

Compounded MMC should be from the FDA-approved MMC product (rather than from a bulk drug substance) in a facility lawfully operating under either Section 503A or 503B of the FD&C Act.

The AAO recommends physicians select a compounding pharmacy accredited by the Pharmacy Compounding Accreditation Board (ACHC, www.achc.org) that "adheres to quality standards for aseptic compounding of sterile medications."[15] When it is clinically necessary to use a compounded drug, the authors recommend sourcing a FDA-approved MMC product rather than a bulk drug substance. It is ultimately the responsibility of the physician to vet the compounding facility to confirm that, even if accredited by ACHC, it is in compliance with the FD&C Act.

>>Preparing for Usp <800>: a Resource Toolkit

WEBSITES

- Occupational Safety and Health Administration. Safety and Health Topics. Hazardous Drugs. **www.osha.gov/SLTC/hazardousdrugs/index.html**
- Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. **www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardous-drugs.html**
- The USP Compounding Compendium 2019, which includes USP <800>. **www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare**
- USP <800> "Frequently Asked Questions." **www.usp.org/frequently-asked-questions/hazardous-drugshandling-healthcare-settings**
- A USP <800> updates newsletter. **www.usp.org/HQS-Signup-Form**
- National Institute for Occupational Safety and Health. NIOSH alert: preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. **www.cdc.gov/niosh/docs/2004-165/**
- The NIOSH List of Antineoplastic and Other Hazardous Drugs in Health Care Settings, 2016. **www.cdc.gov/niosh/docs/2016-161 /pdfs/2016-161.pdf**
- NIOSH Safety and Health Topics: Hazardous Drug Exposures in Healthcare: Antineoplastic Agents. **www.cdc.gov/niosh/topics/hazdrug/antineoplastic.html**
- NIOSH Safety and Health Topics: Occupational exposure to antineoplastic agents and other hazardous drugs: Effects of occupational exposure. **www.cdc.gov/niosh/topics/hazdrug/effects.html**

TEXT

- Pharmaceutical compounding-sterile preparations (general information chapter 797). In: The United States pharmacopeia, 39th rev., and the national formulary, 34th ed. Rockville, MD. *United States Pharmacopeial Convention.* 2016:626-670.
- American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm.* 2018;75:1996-2031.

CONCLUSION

MMC and 5-FU are frequently used in glaucoma surgery with great success. Both drugs can be safe, even though they are most often used off label. Physicians should review their own state pharmacy board website for statutory regulations regarding compounding drugs, outsourcing compounded products, and requirements for outsourcing facilities. It is the ultimate responsibility of the health care provider ordering, preparing, and administering a drug to assure that it was prepared and administered in compliance with state and federal regulations. ■

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2. Li NYK, Chen F, Dikkers FG, et al. Dose-dependent effect of mitomycin C on human vocal fold fibroblasts. *Head Neck*. 2014;36(3):401-410.
3. Liu W, Wang J, Zhang M, et al. Comparison of subconjunctival mitomycin C and 5-fluorouracil injection for needle revision of early failed trabeculectomy blebs. *J. Ophthalmol*. 2016;2016:1-6.
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7. Caprioli J, Kim JH, Friedman DS, et al. Special commentary: supporting innovation for safe and effective minimally invasive glaucoma surgery; summary of a joint meeting of the American glaucoma society and the food and drug administration, Washington DC. February 26, 2014. *Ophthalmology*. 2015;122(9):1795-1801.
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9. United States Pharmacopeial Convention. USP Compounding compendium 2017. USP <797> pharmaceutical compounding—sterile preparations. Rockville, MD. *United States Pharmacopeial Convention*. 2017;39-82.
10. General chapter pharmaceutical compounding sterile preparations. USP. http://www.usp.org/compounding/general-chapter-797. Accessed April 27, 2019.
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13. Fluorouracil injection, USP [prescribing information]. Irvine, CA. Gensia Sicor Pharmaceuticals; 1999; NA (1193);20.
14. Beans BE. USP <800> adds significant safety standards: facility upgrades needed to protect employees from hazardous drugs. *PT*. 2017;42(5):336-339.
15. Verifying the source of compounded Bevacizumab for intravitreal injections--2014. American Academy of Ophthalmology. Https://www.aao.org/clinical-statement/verifying-source-of-compounded-bevacizumab-intravi-2. Published October 9, 2014. Accessed April 27, 2019.