Review Article

Current Trends in Ophthalmology

Ophthalmic Compounding and Implications of Revised United States Pharmacopeia Chapter 797 Standards

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Abstract

Following the devastating results of the New England Compounding Center debacle resulting from contaminated compounded steroid injections, which occurred in 2012, state and national attention focusing on the safety of compounded sterile products has continued to escalate. The Drug Quality and Security Act (DQSA) was passed, which created voluntary outsourcing facilities under section 503B as a new class of compounders regulated by the FDA. Section 503B compounding follows Current Good Manufacturing Process (cGMP) standards. FDA guidance documents addressing sterile compounding are also continuing to increase in volume and specificity. Traditional compounding efforts under DQSA section 503A remain the purview of state oversight but FDA does reserve the right to intervene at any time for quality concerns. The primary standards for 503A compounding are found in the United States Pharmacopeia (USP) Chapter <797>. These standards are currently under revision and the enhanced standards are scheduled for implementation December 2019. Typically, State Boards of Pharmacy have provided oversight and inspections on compounding but these efforts have been focused mainly on pharmacy operations. Ophthalmic compounding outside of hospital or retail pharmacy settings has gone largely unregulated. However, the revised USP <797> is intended to address all sites providing sterile compounding and eye centers performing these functions will be expected to be in full compliance with the new standards by the implementation date.

Keywords: Vitreal, Periocular, Intraocular, Intravitreal, Uveal scleral routes, Sterile compounding, Voluntary outsourcing facility

Abbreviations: USP: United State Pharmacopeia; FDA: Food & Drug Administration; cGMP: Current Good Manufacturing Processes; SBOP: State Board of Pharmacy

Introduction

Over the last 2 decades in healthcare, the study of ophthalmic medications, including new therapeutic uses, has experienced remarkable growth. Rapid advances in surgical techniques together with discoveries of innovative ophthalmic treatments for ophthalmic disorders, has fueled an increasing need for new drug

formulations and treatment options. Additionally, with an aging population accounting for increased numbers of ophthalmic disorders associated with individuals living longer, the need for continual development of existing and new ophthalmic drug formulations will continue to grow. Prior to the last few decades, the ophthalmic pharmaceutical industry was dominated by two or three companies who marketed a few long-standing

therapeutic drug products such as glaucoma agents, anti-infectives, vasoconstrictors, steroids, diagnostic miotics and mydriatics, and anesthetics. Today, there are an increasing number of products manufactured by many different ophthalmic drug companies for a larger number of treatment disorders. However, as great as the growth in the ophthalmic market has been over the last 2 decades, it has not kept pace with the rapid advances in ophthalmic treatment developments and the demand for drug treatment alternatives associated with these advances.

One reason for this disparity can be attributed to market forces, which often do not support commercial production of an ophthalmic formulation as compared to a systemic dose option. Drug products in the market are driven by profitability potential. Commercial manufacturers, despite the therapeutic need for a product, avoid producing products that do not bring timely and adequate returns on investment. Sales of ophthalmic specialty products will seldom match those of systemic drug products. Additionally, the eye is a complex drug delivery structure with unique formulation considerations which can also increase costs to bring a product to market. For example, one may initially think that the eye is an easy target for drug therapy. It is externally accessible and allows direct application of a drug formulation onto it. However, the physical structure of the eye is a formidable barrier to drug penetration, and formulation design is critical for effective drug delivery, stability, and patient tolerability.

The impact of market forces, profitability, and unique formulation considerations preventing the development of comparable ophthalmic products to systemic treatment options has led to an increasing need for ophthalmic compounding by pharmacy practitioners. The following paper describes anatomical challenges for ophthalmic formulation and compounding, the history of USP 797 and current standards, the impact of USP 797 on ophthalmic compounding, compounding process considerations for ophthalmic products, and restrictions on ophthalmic compounding.

Anatomical challenges in ophthalmology

Key anatomical structures in the eye that can be either barriers to drug delivery or target areas for compounded drug activity include the conjunctiva, cornea, anterior chamber, posterior chamber, uveal scleral region, and retina. Compounded ophthalmic products are delivered through or to any of these structures by different

administration routes, sometimes by more than a single route at the same time. There are four basic routes of administration for compounded products to the eye: 1) topical routes, such as liquids, ointments, or solid inserts; 2) periocular injection routes, including sub conjunctival, sub-Tenon, or retro-bulbar injections (into the posterior region of the orbit); 3) intraocular injection routes (into the aqueous of the anterior/posterior chambers or vitreous in the vitreal chamber through the conjunctiva); and 4) systemic routes, including intravenous, intramuscular, or oral.

Topical administration and treatment involve both surface and intraocular conditions. This route includes the installation of eye drops, application of ointments, gels, or the use of a solid slow release dosage form on the surface of the eye (e.g., contacts, collagen shields). Generally, penetration of compounded drugs across the conjunctival membranes is good but can also be seriously limited due to rapid removal of drug through high perfusion and blood flow properties. Tear film and normal ocular clearance mechanisms create limitations and challenges for topical administration. Under normal circumstances, the ocular surface contains 7-10 microliters of aqueous tear at a time. Most dropper bottles deliver a drop size of 40-50 microliters per drop [1]. Once instilled, the eye surface can briefly hold 20 microliters (about ½ a drop size), until tearing mechanisms due to the sudden increase in surface volume dilute drugs further, and rapidly drain excess volume in an effort to return to the normal volume size of 7-10 microliters. Tear volume typically will return to normal in two to five minutes after instillation. This means that: 1) up to 50% of a compounded drug dose is “lost” on instillation, and 2) contact time for drug concentrations is short and limited. Thus, with compounding topically applied drugs, challenges involving drug delivery, drug removal, effective yet tolerable concentrations, and contact time sufficient to allow absorption and delivery of the drug must be considered. When internal eye structures are involved and challenges for delivery of adequate drug concentrations exist, or when higher concentrations of drug are needed than can be compounded for topical administration, other routes should be considered or should supplement topical administration.

The cornea presents significant challenges which are important to consider for topical ophthalmic products. Drug penetration through the cornea depends on the pharmacological properties of the compounded product and its interaction with each corneal layer. The cornea

consists of 5 different layers in order from outer to inner layer: the epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium [2-6]. The outer most and inner most layers (epithelium, endothelium) possess lipophilic physiochemical properties while the middle three layers (Bowman's, stroma, Descemet's) possess hydrophilic properties. This physiochemical difference affects drug penetration through the cornea to inner structures of the eye. Additionally, the physical structure of each layer has unique qualities to affect penetration as well.

Other factors affecting drug delivery of compounded products include pH of the product, the preservative-free nature of the compounded product, contact surface time, stability of the product, and delivery of the desired drug into targeted chambers (anterior, posterior, vitreal) in effective concentrations to produce desired therapeutic effects. The normal ocular surface pH is 7.4. Drug products that vary from normal pH can cause increased stinging and irritability when instilling into the eye, making the drop less tolerable to patient use. Increased irritability generates tearing mechanisms to clear the irritating drug off the ocular surface of the eye, which can decrease surface contact time which may be necessary for absorption of the drug product. A preservative (principally benzalkonium chloride) not only helps prevent bacterial growth within a product, but also enhances penetration of drug across the corneal membrane through an active transport mechanism. Compounded products, which are typically prepared without preservatives, are subject not only to potential contamination effects from use and decreased sterility time, but also decreased penetration without the active transport effect that a preservative provides.

Compounded product stability affects product delivery to desired structures of the eye and can often be the limiting factor for whether or not a drug can be compounded in an ocular form. For example, ciprofloxacin 0.3% topical drops have been reported to precipitate on the ocular surface of the eye, resulting in delayed healing of corneal infections [7]. This is related to the pH nature of ciprofloxacin (4.5) which varies sufficiently from the normal pH of the eye and results in a precipitate in some patients. Additionally, blood brain barrier effects for drug delivery to the retina and the lack of direct blood flow within the eye contribute to further effects on drug delivery and penetration of ocular preparations.

These multiple factors influencing ophthalmic drug

preparations help explain why the lack of development of commercially desired products has led to an increasing need for ophthalmic compounding by pharmacy practitioners. For example, when anatomical factors prevent topical delivery of drug, compounding drug preparations for direct injection to target areas of the eye (e.g., periocular, intraocular, intravitreal, uveal scleral routes) becomes necessary. Additionally, when a commercial manufacturer for reasons of profitability determines that prescription potential, product demand or expenses to bring a product to market do not justify manufacturing of a drug product, the need for compounding of topical preparations may be necessary. As mentioned previously, with all products, the compounding pharmacy must account for anatomical challenges, patient safety, patient tolerability, drug stability, and as will be discussed further, product sterility and USP 797 compounding requirements.

History of standards up to the current USP <797>

In recognition of the safety impact that compounded sterile products have on patients, in 2004 the United States Pharmacopeia (USP) created Chapter 797 focusing on Pharmaceutical Compounding – Sterile Preparations. Chapter 797 was revised in 2008 and is currently under revision again with an anticipated implementation date of December 2019. It is important to note that all USP chapters that fall below 1,000 can be enforced by the FDA, surveyed against by The Joint Commission and adopted fully or in part by regulatory bodies such as State Boards of Pharmacy.

In creating Chapter 797, USP recognized that millions of medications are compounded each year in the US to meet the unique needs of patients. Compounding provides access to medications for patients who may not be able to use commercially available formulations due to dosing requirements, allergies or rare diseases. Many of these compounded medications are required to be sterile, and that includes medications administered by injection, intravenous infusion (IV), intraocular (injection in the eye) or intrathecal (injection in the spine).

USP Chapter 797 is intended to help practitioners understand the risks inherent in sterile compounding and to establish standards for patient safety to help prevent compounding of drugs that are sub-potent, super potent or contaminated, exposing patients to significant risk of adverse events or even death. USP standards for preparing compounded sterile drugs help to reduce risks

of contamination, infection or incorrect dosing. It is also important to note that USP 797 is not just a “pharmacy standard”. This standard applies to sites other than pharmacies such as ophthalmic surgery centers.

USP 797 and ophthalmic products

How USP risk levels impact ophthalmic products: USP <797> currently sets compounding risk levels at Low/Medium/High based on the likelihood of contaminating a compounded sterile preparation (CSP) with microorganisms, spores, endotoxins or other foreign material. Different rules apply to the compounding process depending on the level of risk. Low Risk generally involves compounding with aseptic manipulations using only sterile ingredients, products and devices in ISO Class 5 or higher air quality. Medium Risk generally includes compounding or pooling multiple doses of sterile products for administration to multiple patients or to a single patient on multiple occasions. The compounding process involves more than single volume transfer or requires an extended period of time for compounding. High Risk compounding generally involves the use of non-sterile ingredients or devices to ultimately produce a sterile final product.

When compounding ophthalmic products, in the absence of the product being part of an investigational study, it is important that the compounded product be supported by evidence of use in humans and tested/proven formulation recipes. Whether for diagnostic or therapeutic use, recipes for formulations referred to as Master Formulation Records (MFR) per USP <797>, should be supported in the medical literature and conform to accepted standards of care in ophthalmology and pharmacy practice [8]. Indications and use of compounded formulations must always protect patient safety, provide sound data on stability and sterility, and provide methods of compounding that maintain the highest standards of quality possible for use in patients.

Low risk compounding of ocular drug preparations typically involves reconstitution per package insert directions for manufacturer prepared products, or simple drug transfers of non-ophthalmic indicated products to sterile droppers. Low risk compounds primarily include topical drop formulations and the use of sterile ophthalmic eye droppers. Medium risk compounding involves both transfers and dilutions of more than a single drug product, including combination of sterile non-ophthalmic indicated solutions with limited manipulations (no more than two) and no more than three

different drug products per USP <797> [8]. Medium risk compounds comprise all ocular routes of administration including topical, periocular, and intraocular routes.

High risk compounding involves the preparation of drug product from raw/non-sterile chemicals, including transfers and dilutions, combination of multiple ingredients, and multiple/complex manipulations throughout the compounding process. High risk compounding presents the highest risk to patient safety and potential adverse events and must be based on sound evidence based medical practice. Typically, high risk compounds are limited to intraocular injections, but may also include topical preparations with multiple manipulations, dilutions, or drug products. Unlike low and medium risk compounding, high risk compounding requires sterilization of the final product prior to use in patients by an acceptable and appropriate method of sterilization. USP <797> provides acceptable methods of sterilization for high risk compounding, and methods used should be based on the type of product being compounded and the ability to sterilize the product without compromising the quality of the final product itself. In ophthalmic compounding, the commonly accepted sterilization method involves filter sterilization using a 0.22-micron filter of the product into a sterile vial, dropper, or container. High risk compounding also includes the use of human derived products prepared from a patient’s serum or blood, such as the preparation of autologous serum tears for the use in treating patients with dry eye disease [9]. Examples of low, medium, and high risk compounded ophthalmic products can be seen in table 1.

Ophthalmic compounded sterile products and the importance of USP <797>

Ophthalmic products demand sterility due to the nature of the products and the methods by which they are administered in the eye. Because the nature and function of the eye demands low to no blood flow within the eye itself, compounded sterile products (CSPs) must be of the utmost sterility to prevent adverse events from occurring due to contamination and introduction of potential infectious organisms into the eye. When a physician administers a compounded medication, there must be a very high level of assurance that it is accurately compounded in a process that renders it free from microbial contamination and dangerous impurities [10].

Infectious organisms are mainly bacterial or fungal in nature. These infections develop due to introduction

Table 1: Examples of compounding per risk level (not a comprehensive list).

Ophthalmic Compounding Risk Levels		
Low Risk	Medium Risk	High Risk
Acetylcysteine Topical Drops •Alkali burns, KCS, corneal melt	Amikacin Topical Drops •Bacterial Infection	AlteplaseIntravitreal •Intraocular fibrin deposits
Amikacin Topical Drops •Bacterial infection	Amphotericin B Topical Drops •Fungal/yeast infection	Amphotericin B Subconj./Intravit. •Fungal/yeast infection
Ascorbic Acid Topical Drops •Corneal alkali burns	Bacitracin Topical Drops •Bacterial infection	Autologous Serum Topical Drops (Tears) •KCS (Dry Eye Syndrome)
Clindamycin Top./Subconj •Bacterial Infection	Cefazolin Top./Subconj. •Bacterial Infection	Cefazolin Intravitreal •Bacterial Infection
Edetate Disodium Topical Drops •Corneal band keratopathy, lime injury	FoscarnetIntravitreal •CMV Retinitis	CeftazidimeSubconjunctival/Intravitreal •Bacterial Infection
Fluorouracil Topical Drops •Glaucoma, pterygium	Tobramycin Topical Drops •Bacterial Infection	Clindamycin Intravitreal •Bacterial Infection
Gentamicin Fortified Drops •Bacterial Infection	Vancomycin Top./Subconj. •Bacterial Infection	Cocaine Topical Drops •Diagnosis Horner's Syndrome
Dexamethasone Subconj./Intravit. •Ocular Inflammation	Chlorhexidine Topical Drops •Acanthamoeba Keratitis	Cromolyn Topical Drops •Allergic Conjunctivitis
	Medroxy-progesterone Topical Drops •Corneal Alkali Burns, Dry Eye Disease	Fluorouracil Subconj./Intravit. •Glaucoma, Retinal Detachment, Premalignant Lesions
	Tissue Plasminogen Activator (TPA) Intravit. •Intraocular Fibrin	Mitomycin Topical Drops •Pterygium, Glaucoma
		Tobramycin Intravitreal •Bacterial Infection
		Vancomycin Intravitreal •Bacterial Infection
		PolyhexamethyleneBiquanide Topical Drops •Acanthamoeba Keratitis

Topical Drop = Top.

Subconjunctival Injection= Subconj.

Intravitreal Injection = Intravit.

of bacteria either topically or intraocularly. Some possible causes include 1) failure to sterilize the injection site adequately, resulting in contamination from an injection site source, 2) ocular trauma, where internal compromise of the eye and bacterial introduction may occur, 3) ocular surgery where the surgical wound itself does not seal timely or properly allowing micro-leaks of bacterial infiltrates intraocularly, 4) touch contamination by the patient either by habit or poor postoperative drop administration technique, and 5) substandard and poor compounding of ophthalmic products (topical or injection).

Eye droppers act as a potential growth medium enhancer for fungal and bacterial organisms. A lack of preservative common to compounded topical drops can allow proliferation of microbial organisms unlike that of manufactured commercial preparations which contain preservatives. During the compounding process, substandard or poor compounding methods and not adhering to USP <797>, including insufficient sterilization of the CSP prior to dispensing for use, increase the likelihood of microbial contamination and potential infection development. Conversely, for intraocular use, when ophthalmic CSPs are administered directly into low blood flow areas, the normal infectious defense response

is decreased because coping mechanisms (leukocytes-“white blood cells”) for fighting bacterial infection are lessened due to the low blood flow of the eye. Infectious organisms introduced through contaminated CSPs can proliferate “un-checked” in such a closed system such as the eye. This proliferation can lead to serious sight-threatening infections such as endophthalmitis [11].

Thus, in both topical and intraocular use CSPs, the importance of adherence to quality standards and processes for compounding, achieved through understanding and following guidelines described by USP <797>, cannot be over-emphasized when it comes to ophthalmic compounded products. USP <797> standards applied to compounding of ophthalmic products provides safe, effective, useful, and quality drug preparation options to meet patient needs for treating eye conditions they are intended for.

In a recent article from The Pew Charitable Trust the importance of careful ophthalmic compounding was reinforced with a report on problems encountered in Dallas, Texas last year. Dozens of people reported symptoms such as vision impairment, poor night vision, and loss of color perception after they received eye injections of compounded antibiotics during cataract surgery. The Food and Drug Administration (FDA) later issued a safety alert that said the drug was made with a large amount of an inactive ingredient that apparently degraded as the drug was prepared and resulted in the observed adverse effects [12].

Rules and considerations in compounding ophthalmic products

It is important for the ophthalmic professional compounding sterile products (CSPs) to understand rules governing how CSPs must be prepared under sterile and safe conditions, as well as whether the product is hazardous or non-hazardous. Hazardous CSPs pose a danger and health risk to the person preparing the CSP, those who handle or administer the CSP to patients, and to the patients themselves. Because of this exposure risk, hazardous CSPs must be prepared in primary engineering controls such as biological safety cabinets or Compounding Aseptic Containment Isolators (CACIs). These engineering controls isolate and protect the compounder and create an ISO 5 air quality environment for sterile product manipulation while performing compounding of the CSP. USP <797> provides detailed description for processes in compounding and standards for primary engineering controls to be used [8]. Precautions for transporting,

handling, and administering these products must be followed. Additionally, the safe disposal of all waste products and CSPs to be wasted must be in accordance to waste stream standards put forth by USP <797>. It is the responsibility of all health care providers and pharmacy professionals to understand the risks, build and provide compounding facilities and equipment that comply with USP <797> to meet patient needs, and establish policies and procedures that are designed to protect and ensure the safe use of hazardous CSPs for all patients and staff prior to their use.

Non-hazardous CSPs require different processes for compounding depending on the risk level. As mentioned before, Low Risk generally involves compounding with aseptic manipulations using only sterile ingredients, products and devices in ISO Class 5 or higher air quality. This risk level may also involve reconstitution only, and may therefore be compounded in a sterile promoting, clean, designated medication preparation area, or at patient bedside if the product will be immediately administered (within 1 hour). Medium Risk CSPs require a higher standard for sterile preparation and requires the use of sterile compounding isolators (hoods) such as a Laminar Airflow Workbench (LAFW) or Compounding Aseptic Isolator (CAI). These devices are designed to maintain an ISO Class 5 or higher air quality standard, and when used properly, help to ensure that the CSP is sterile and safe for use in patients. High Risk compounding requires the highest level of sterile processes, due to the use of non-sterile products, in order to produce a sterile and safe product for patient use. CSPs which are categorized as High Risk require the use of Compounding Aseptic Isolator device (CAI), and require a sterilization process (e.g., filter sterilization) for the final product before using safely in patients.

Restrictions to compounding ophthalmic products

Before compounding any ophthalmic product, it is important to consider 5 criteria that may restrict the compounding of a specific product.

Market place factors: Market forces imply any legal restrictions on compounding of the specific product. It is unlawful to compound any product which is marketed or manufactured by any organization which owns a patent or control over a chemical product. Failing to adhere to these restrictions can result in heavy fines and penalties to the compounding entity.

Cost and facility set up: The cost of compounding an ophthalmic product is largely controlled by the level of risk the CSP has and the necessary facility set up and equipment necessary to properly prepare it. If a CSP is not economically feasible, or a facility is not set up properly to prepare it according to the USP risk level, then it should not be considered for preparation.

Safety and efficacy in patient use: CSPs for ophthalmic consideration must not only be safe to use, but they also must demonstrate efficacy in treating the disease for which it is intended.

Supporting documented evidence and references for use: Evidence based medicine is key to the use of compounded products in ophthalmology. Documented evidence supporting stability of the product and the storage conditions associated with it, sterility data to support sterile use, and evidence supporting the use in humans must be compiled and maintained on record for any ophthalmic CSP being prepared.

USP <797> formulation requirements: USP outlines specifically what must be documented and recorded for all CSPs produced. A Master Formulation Record (MFR) describes all necessary information which must be gathered and maintained for all ophthalmic CSPs produced. If this information is lacking, the CSP should not be prepared.

Conclusion

Compounded ophthalmic drugs represent an opportunity to enhance patient care by creating unique formulations of medications that are not available commercially and that are tailored to the needs of individual patients. However, compounding sterile products also comes with the risk of contamination and large content errors, which can cause serious adverse events for patients. To date, the regulation of sterile compounding activity has largely been the purview of State Boards of Pharmacy inspectors and their work has been directed exclusively toward pharmacies. But the requirements of USP Chapters 797 and 800 apply to ALL sites and not just pharmacy, and the FDA can step-in at any time as can other state regulatory agencies. All sites performing compounding of ophthalmic medications would be well advised to understand the requirements in the current Chapter <797>, as well as what is coming in December 2019 with the Revised Chapter <797> and the new Chapter <800>, and the implications on compliance for their operations. A comprehensive review and gap

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analysis against current and proposed standards should be in place as an initial step for all sites compounding ophthalmic medications.

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