May 25, 2018

Scott Gottlieb, MD
Commissioner
Food and Drug Administration
Attn: Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-D-1067 for "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act."

Dear Dr. Gottlieb:

The American Society of Cataract and Refractive Surgery (ASCRS) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act."

ASCRS is a medical specialty society representing nearly 9,000 ophthalmologists in the United States and abroad who share a particular interest in cataract and refractive surgical care. ASCRS members annually perform the vast majority of cataract procedures in the United States.

ASCRS members rely heavily on the use of compounded drugs to treat patients. Therefore, ASCRS is very concerned that this draft guidance may limit access to necessary ophthalmic compounded drugs from 503B outsourcing facilities, many of which must be compounded from bulk substances. **ASCRS is providing comments on several aspects of the draft guidance on bulk drug substances compounded in 503B outsourcing facilities, including:**

- **Opposition to the FDA draft guidance, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act," which will severely impact patient care and safety, as it is not possible to compound many ophthalmic drugs using bulk drug substances that are components of FDA-approved drugs;**

- **Significant concerns this proposal and the FDA requirement for "clinical need" disrupt a patient's treatment plan by allowing the FDA, rather than the prescribing physician, to make the final determination of what is clinically needed which may further exacerbate existing barriers to accessing ophthalmic drugs from 503B outsourcing facilities;**

- **Concern that this proposal disincentivizes compounders from registering as 503B outsourcing facilities and, therefore, will limit access to compounded drugs from 503B outsourcing**

facilities that follow Current Good Manufacturing Practice (CGMP) regulations designed to help assure the safety and efficacy of drug products.

- **Recommendations of specific bulk drug substances that must be on the FDA 503B Bulk List to ensure continued physician and patient access to sight-saving ophthalmic drugs.**

Our full comments on these issues are provided in detail in the following:

Patient Safety Issues Raised by Use of Bulk Drug Substances that Are Components of FDA-Approved Drug Products

ASCRS is concerned that the proposal to use a bulk drug substance that is a component of an FDA-approved drug product for compounding will pose significant threats to patient safety and ocular health because there are many situations in which ophthalmologists need drugs compounded from the original bulk substance. Many approved drug products do not have the same strength, routes of administration, or formulation needed to treat ocular disease. For example, ophthalmologists typically use moxifloxacin injections to prevent and treat ophthalmic infections. However, the FDA-approved formulation is a 400mg/250ml product, which is a lower concentration than is required for ophthalmic use and must be compounded. It is not possible to produce the required concentration for the ophthalmic product without compounding from a bulk drug substance.

Furthermore, not all bulk drug substances will be the same when compounded from the FDA-approved drug due to the excipients in the product. For instance, it is common for ophthalmologists to prescribe postoperative eye drops that are a combination of a nonsteroidal anti-inflammatory drug (NSAID) drop, such as bromfenac, and a flouroquinolone drop, like Gatifloxacin. Bromfenac requires a very basic pH of about 8.3, and the flouroquinolone requires an acidic pH of about 4.5 for maximum stability. If a compounder were to combine these two FDA-approved products, the bromfenac will likely precipitate, becoming very unstable and, as a result, will be inappropriate for ocular use. Also, the excipients for the two FDA-approved products will have very different profiles, including buffer systems, antioxidants, surfactants, and osmotic agents. Thus, the drug product profile is unique to each product and formulated in a way to maximize stability. Combining the two FDA-approved products rather than using the bulk drug substance would make the resultant product very unstable. More importantly, it is extremely risky to simply combine the two FDA-approved products because there are many unknowns in terms of resultant pH, stability, and osmolality that could lead to dangerous drug interactions that may have the potential to harm patients.

- **Therefore, it is vital that 503B outsourcing facilities have access to important bulk substances to compound from rather than use the FDA-approved product.**

We urge the FDA to recognize the necessity of bulk drug substances when compounding ophthalmic drugs. If 503B outsourcing facilities are unable to use the most appropriate bulk drug substance for compounding, then patients' treatment options will be limited. We urge the FDA to recognize that there are many situations in ophthalmology where it is not appropriate to compound from bulk drug substances that are components of FDA-approved drug products.

FDA's Assessment of "Clinical Need" Could Exacerbate Existing Access Barriers to Ophthalmic Drugs from 503B Outsourcing Facilities

ASCRS is very concerned that current issues physicians face in accessing compounded drugs from 503B outsourcing facilities will be exacerbated by the FDA's proposal for assessing the clinical need for a drug to be compounded from a bulk drug substance. Since the enactment of the DQSA, ASCRS has received dozens of reports from our members describing access issues to certain drugs from 503B outsourcing facilities. Through recent guidance documents, it is obvious that the FDA has ignored comments from outsourcing facilities, specifically smaller facilities expressing their inability or lack of willingness to compound in the small quantities needed by many ophthalmologists, particularly for office use. FDA's final guidance for 503A compounding pharmacies requires a patient-specific prescription for compounded medications from 503A traditional compounders. As an alternative, physicians may obtain compounded medications for office use from a 503B outsourcing facility. However, since drugs for emergent conditions are not used in ophthalmic practices on a regular basis, physicians generally order smaller quantities, which make it less cost-effective for the outsourcing facilities to produce. As a result, many outsourcing facilities do not produce in the requested quantities as indicated in recent FDA reports. **Therefore, FDA's actions in implementing the DQSA have already limited drug access for ophthalmologists from 503B outsourcing facilities.**

503B Outsourcing Facilities Compounding Production Report

Not only are ophthalmologists reporting a lack of access to drugs from 503B facilities, FDA's own reports demonstrate it. In 2016, FDA finalized the guidance, "Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Solution," which requires 503B outsourcing facilities to submit reporting data on drug production. While ASCRS appreciates the FDA's steps toward transparency in drug availability, we remain very concerned that the most recent report finds that a number of ophthalmic drugs are missing from the list of available drugs or are not being produced in the small quantities needed by an ophthalmologist.[1]

Additionally, the report indicates that some ophthalmic compounded drugs are being produced by only one facility. The dependence on one facility to produce compounded drugs needed in ophthalmology is particularly alarming, as it leaves the patient and physician community without access to the drug if there is any disruption in production.

To demonstrate the limited supply of compounded drugs from 503B facilities, please see appendix A of this letter, which includes a list of more than 100 ophthalmic drugs produced by a 503A traditional compounder before the enactment of the DSQA. Today, that same pharmacy has been converted to a 503B outsourcing facility and now produces just a handful of ophthalmic drugs.

ASCRS is concerned that these drug access issues will be made even worse by the FDA's assessment and determination of "clinical need." According to the draft guidance, the FDA will publish a list of bulk drug substances for which there is a clinical need and the rationale for the final determination. We contend that any bulk drug substance that is in an FDA-approved drug means that it has already shown a clinical need.

[1] Upon request, ASCRS will provide a list of ophthalmic compounded drugs not being produced by 503B outsourcing facilitates.

Additionally, ASCRS is alarmed that this proposal takes away the clinical decision making from the physician. According to the draft guidance, the FDA, rather than a patient's physician, will be the ultimate clinical decision maker for what drug is determined "clinically needed" to treat the patient. There are many situations, considered standard of care, in which ophthalmologists need to use bulk drug substances rather than components of an FDA-approved product based on a patient's treatment plan. For example, there are numerous studies indicating that glaucoma patients should use preservative-free compounded medications to prevent ocular cellular damage and inflammation if the drug will be used long-term. However, the majority of FDA-approved glaucoma drops are not preservative free. This is problematic for glaucoma patients who need to use drops long-term, as the toxicity of preservatives causes permanent scarring changes in the cornea and conjunctiva. This also leads to a greater failure rate for subsequent procedures to control glaucoma. Obtaining glaucoma medications without preservatives requires bulk drug substances because the concentrations of each active pharmaceutical ingredient (API) must be adjusted and because preservatives cannot be extracted from FDA-approved products.

- **We urge the FDA to leave clinical decision making up to physicians and ensure access to important bulk drug substances used for compounding in 503B facilities.**

Ensuring Ophthalmologists' and Patients' Access to CGMP Compounded Drugs from 503B Outsourcing Facilities

ASCRS is also concerned that by further limiting how 503B outsourcing facilities can compound, many will decide to limit drug production or even unregister as 503B outsourcing facilities altogether. Currently, 503B outsourcing facilities must adhere to many stringent requirements to be compliant with the Federal Food, Drug, and Cosmetic (FD&C) Act, including complying with the current good manufacturing practice (CGMP) requirements, be inspected by FDA according to a risk-based schedule, and must meet other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound. According to the FDA, 503B outsourcing facilities have higher assurance of safety for their compounded drugs than those made by 503A traditional compounders because they are produced in facilities that adhere to CGMP requirements. It seems that this guidance is in direct conflict with recent initiatives announced by the FDA. FDA Commissioner Scott Gottlieb, MD, announced that the agency is working on a new policy that would encourage compounding of better quality drugs under DQSA by incentivizing 503A traditional compounders to register as a 503B outsourcing facility.[2] ASCRS is concerned that this guidance is in direct conflict with the goals of the agency and disincentivizes compounding from CGMP facilities, as it restricts their ability to compound.

[2] Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to encourage compounding of better quality drugs under DQSA and help healthcare professionals access compounded medications needed for patient care from outsourcing facilities. www.fda.gov September 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577590.htm. Accessed May 9, 2018.

ASCRS has heard serious concerns from outsourcing facilities indicating that if their bulk substances are excluded from the 503B Bulks List, then there will likely be many ophthalmic medications that 503B facilities will no longer be able to compound. **We urge the FDA to prioritize patient needs and ensure that physicians and patients continue to have access to compounded medications from 503B facilities that have a higher assurance of safety.**

Preserving Physician and Patient Access to Drugs Compounded from Bulk Substances by 503Bs.

We strongly urge the FDA to prioritize the needs of patients by preserving physician access to drugs compounded from bulk substances from 503B outsourcing facilities by including a number of bulk drug substances on the 503B Bulks List. To ensure ophthalmologists are able to secure necessary compounded treatments for their patients, ASCRS has compiled a list of bulk drug substances, found in appendix B, that should be included on the 503B Bulks List and explanations for their inclusions. Including these drugs on the 503B Bulks List will ensure the continued availability of necessary ophthalmic compounded drugs. **We encourage the agency to include these drugs on its final list and recognize that access to bulk drug substances for compounding is not only essential to the practice of medicine, but also a vital tool for patient care.**

ASCRS appreciates the opportunity to provide comments regarding proposed changes to the regulations governing "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act." We support the agency's efforts to improve safety issues surrounding outsourcing facilities and look forward to continuing to be a part of the process. We would be pleased to provide further input or clarification of our comments, as needed. Please contact Allison Madson, manager of regulatory affairs, at 703-591-2220 if you have any questions or would like to arrange a meeting.

Sincerely,

Thomas W. Samuelson, MD
President, ASCRS

APPENDIX A: LIST OF OPHTHALMIC DRUGS/INJECTABLES CURRENTLY BEING COMPOUNDED AT A FACILITY THAT IS NOW 503B

Intravitreal Injections
Bevacizumab 2.5 mg/0.1 mL (25 mg/mL) (repackaged, injection)
Cefuroxime 10 mg/mL in 0.9% Sodium Chloride (Preservative-Free)
Moxifloxacin 1 mg/mL in Sterile Balanced Salt Solution (BSS)
Intraocular Injections
Moxifloxacin 5 mg/mL in Sterile Water for Injection
Lidocaine HCl 1%/Phenyleprhine 1.5% in sterile water for injection
Ophthalmic Solutions
Atropine Sulfate 1% in 0.9% Sodium Chloride (Preservative-Free)
Edetate Disodium 3% in Sterile Water for Injection
Mitomycin 0.02% (0.2 mg/mL) in Sterile Water for Injection
Topical Dilation Agents
Cyclo 1% / Trop 1% / Phen 2.5% in sterile water for injection
Tropicamide 1% / Phenylephrine 2.5% in Sterile Water for Injection

LIST OF OPHTHALMIC DRUGS/INJECTABLES BEING COMPOUNDED FROM SAME FACILITY AVAILABLE IN 2013

Anti Allergy Solutions
Cromolyn 4% Preserved or Preservative Free Ophthalmic Solution $73.05/10ml
Naphazoline HCL Preservative Free Ophthalmic Solution $65.65/10ml
Naphazoline/Pheniramine Preservative Free Ophthalmic Solution $65.65/10ml
Pheniramine 0.3% PF Ophthalmic Solution $65.65/10ml
Zinc Sulfate 0.25% Preservative Free Ophthalmic Solution $50.85/10ml
Anti-Infectives
Antibiotics
Amikacin Ophthalmic Solution 10-50mg/ml $97.20/10ml
Azithromycin 2mg/ml PF Ophthalmic Solution $102.60/10ml
Azithromycin 1% PF Ophthalmic Solution $102.60/10ml
Bacitracin 400u/gm/Dexamethasone 0.05% Oph Ointment $63.20/4gm
Bacitracin Ophthalmic Solution 5,000 or 10,000 u/ml $53.30/10ml
Cefazolin Ophthalmic Suspension $77.95/10ml
Ceftazidime Ophthalmic Solution $82.90/10ml
Chloramphenicol 0.5% Preservative Free Ophthalmic Solution $82.90/10ml
Chloramphenicol 1.0% Ophthalmic Ointment $77.95/4gm
Chlorhexidine Ophthalmic Solution $63.20/10ml
Clindamycin Preservative Free Ophthalmic Suspension varies
Clindamycin 1% Ophthalmic Ointment varies
Ciprofloxacin 0.3% Preservative Free Ophthalmic Solution $65.65/10ml
Clarithromycin 1% Ophthalmic Suspension $90.30/10ml
Doxycycline 0.025% or 0.1% Oph Solution $53.30/10ml
Fortified Cefazolin Ophthalmic Suspension $77.95/10ml
Fortified Gentamicin Ophthalmic Solution (also available Preservative Free) $64.40/7ml
Fortified Tobramycin Ophthalmic Solution (also available Preservative Free) $64.40/7ml

Fumidil B (bicyclohexylammonium fumagillin) $103.10/10ml
Gentamicin Preservative Free 3mg/ml Oph Solution $53.30/5ml
Imipenium/Cil 5mg/ml Pf Oph Solution $102.60/10ml
Kanamycin Ophthalmic Solution 40mg/ml $44.15/10ml
Levofloxacin 5-25mg/ml Ophthalmic Solution $53.30/10ml
Metronidazole 0.5% Preserved or Preservative Free Ophthalmic Solution $66.15/10ml
Metronidazole 0.75% Ophthalmic ointment $68.10/4gm
Neomycin 15mg/ml Ophthalmic Suspension $41.00/10ml
Paromycin 15mg/ml Ophthalmic Solution $102.60/10ml
Penicillin G Potassium Ophthalmic Solution $83.40/10ml
Piperacillin 10mg/ml Pf Oph Solution $117.40/10ml
PHMB 0.01% or 0.02% $92.75/15ml
Polymixin/Trimethoprim Preservative Free Ophthalmic Solution $102.60/10ml
Sodium Sulfacetamide 10%-30% Preservative Free Ophthalmic Solution $82.90/10ml
Sulfamethoxazole/Trimethoprim Ophthalmic Solution $65.65/10ml
Vancomycin 20mg/ml, 25mg/ml or 50mg/ml Ophthalmic Solution $77.95/10ml
Vancomycin 14mg/ml preservered (60 day exp date) $35/10ml
Tobramycin 0.3%/Dexamethasone 0.1% Oph Solution $65.65/5ml
Tobramycin 0.3% Preservative Free Oph Sol $77.95/10ml
Tetracycline 1% Preservative Free Oph Ointment $82.90/4gm

Anti-virals

Acyclovir 3% Ophthalmic Ointment $92.75/4gm
Cidofovir Ophthalmic Solution (Release is required) $225.85/3ml
Idoxuridine 1% or 0.1% Ophthalmic Solution $75.40/8ml
Idoxuridine 0.5% Ophthalmic Ointment $73.05/4gm
Trifluridine 1% Preservative Free Ophthalmic Solution $108.15/8ml
Trifluridine 0.5% Compounded Ophthalmic ointment $73.60/4gm
Vidarabine 3% Ophthalmic Ointment $92.35/4gm

Anti-fungals

Amphotericin 0.1-0.5% Ophthalmic Solution $77.35/10m
Clotrimazole 1% Ophthalmic Suspension $77.95/10ml
Fluconazole 2mg/ml Ophthalmic Solution $90.30/10ml
Flucytosine 10mg/ml Ophthalmic Solution $65.65/10ml
Itraconazole 1% Ophthalmic Suspension $78.95/10ml
Ketoconazole 5% Oph Suspension in Peanut oil $77.95/10ml
Micafungin 0.1% Oph Solution $144.25/5ml
Miconazole Nitrate 1% Ophthalmic Suspension $90.30/10ml
Natacyn Ophthalmic Suspension $231.52/15ml
Voriconazole 1% Cmpd Ophthalmic Solution $157.50/10ml

Cytotoxic Agents

Fluorouracil Ophthalmic Solution 1% $53.30/10ml
Thiotepa 1:2000/ 1:1000 Oph Solution $77.95/5ml
Mitomycin Injection or Ophthalmic Solution (all strengths) $45.52/1ml

Diagnostic Agents

Cocaine Ophthalmic Solution 4% & 10% Varies
Fluorescein Oph Solution 0.2% - 2% Preserved or Preservative Free $41.00/15ml

Glycerin 99.5% PF or Preserved Ophthalmic Suspension $32.06/10ml
Gonioscopic Gel (various strengths) $32.06/10ml
Hydroxyamphetamine 1% Preserved or PF 5ml $53.30/5ml
Lissamine Green 1% Preservative Free or Preserved Ophthalmic Solution $32.06/10ml
Rose Bengal Solution 1% Pres. Free or Preserved Ophthalmic Solution $41.00/10ml
Saccharin Sodium 10mg/ml $41.00/10ml
Sodium Saccharin 2% Ophthalmic Solution $41.00/10ml

Dry Eye Compounds

Albumin 5% Ophthalmic Solution $53.30/10ml
Aquasol A Ophthalmic Suspension $83.45/15ml
Calcium Carbonate 10% Ophthalmic Ointment $41.00/30gm
Castor Oil 2% Ophthalmic Suspension $32.06/10ml
Cyclosporine 0.2% Ophthalmic Ointment $62.65/4gm
Cyclosporine 0.05% in Cyclodextran Solution $83.35/10ml
Cyclosporine 0.05% /Dexamethasone 0.01 % in Cyclodextran Solution $90.30/10ml
Cyclosporine 0.05-2% Ophthalmic Suspension in Gum Cellulose varies
Dehydroepiandrosterone (DHEA) Ophthalmic Suspension 0.5% or 1% $90.30/10ml
Dextran Ophthalmic Suspension $32.06/10ml
Estradiol 0.01-0.03% Ophthalmic Suspension $93.75/10ml
GumCellulose Preservative Free Ophthalmic Solution 0.3% to 2.5% $16.00/15ml
Hyaluronic Acid PF Ophthalmic Suspension 0.5% $144.55 /10ml
Methylcellulose Preservative Free Ophthalmic Solution $16.00/15ml
Poly-Vinyl Alcohol/ Povidone Ophthalmic Solution $32.06/10ml
Rapeseed Oil 2% (Alpha Omega Drop) Suspension $32.06/10ml
Retinoic Acid (all trans) 0.01% Ophthalmic ointment $78.35/4gm
Retinoic Acid (all trans) 0.01% or 0.005% Ophthalmic Suspension $78.35/10ml
Serum Ophthalmic Drops varies
Sodium Carboxy Methylcellulose Ophthalmic Gel $16.00/15ml
Tacrolimus 0.02% Cmpd Ophthalmic Suspension $32.06/5 ml
Tacrolimus 0.02% Cmpd Ophthalmic Ointment $67.00/4 gm
Trehalose 3.78% Ophthalmic Solution $73.05/10ml
Vaseline Preservative Free Ophthalmic Ointment $78.55/4gm
Vitamin A 0.01% Oph Suspension (All Trans Retinoic Acid) $77.95/10ml
Vitamin A 0.01% Ophthalmic Ointment (All Trans Retinoic Acid) $78.35/4gm

Glaucoma

Acetazolamide 1% Preservative Free Ophthalmic Suspension $102.60/10ml
Apraclonidine Preservative Free ** Ophthalmic Solution $77.95/5ml
Betaxolol 0.125% Preservative Free** Ophthalmic Solution $53.30/5ml
Bimatoprost 0.015% PF** Ophthalmic Solution $107.55/3ml
Brimonidine 0.1% or 0.075% Preservative Free** Ophthalmic Solution $102.60/10ml
Brinzolamide 0.5% PF** Ophthalmic Solution $45.95/5ml
Carbachol 1.5%, 2.25% & 3% Preservative Free Ophthalmic Solution $90.30/10ml
Clonidine Preserved or Preservative Free Ophthalmic Solution $65.65/10ml
Dipivefrin 0.1% Pres'd or Pf Oph Solution $55/5ml, $75.00/10ml
Dorzolamide 1% PF** Ophthalmic Drops $102.60/10ml
Dorzolamide 1%/Timolol 0.25% PF ** Ophthalmic Solution $97.2010ml
Epinephrine Bitartrate Preservative Free Ophthalmic Solution $74.35/10ml
Epinephrine Borate Preservative Free Ophthalmic Solution $97.20/10ml
Epinephrine HCL 1% Preserved Ophthalmic Solution $77.95/10ml

Latanoprost 0.0025% Preservative Free** Ophthalmic Solution $90.07/3ml
Levobutanol 0.25% PF** Ophthalmic Solution $53.30/5ml
Phospholine Iodide (all strengths) varies
Pilocarpine Preservative Free Ophthalmic Solutions 0.1% to 6% $65.65/10ml
Pilo 1%/Epi 1% Cmpd Ophthalmic Solution $41.00/5ml
Travoprost Z 0.002% Cmpd PF** Ophthalmic Suspension $83.35/3ml
Preservative Free Steroids
Dexamethasone Na Phos Injection 4-24mg/ml PF varies
Dexamethasone Sodium Phosphate Preservative Free Solutions $58.00/10ml
Dexamethasone 0.05% Ophthalmic Ointment $82.90/4gm
Dexamethasone 0.05% Lanolin Free Ophthalmic Ointment $82.90/4gm
Fluorometholone 0.1% PF Ophthalmic Suspension $55.00/5ml
Loteprednol 0.25% PF** Opthalmic Solution $74.35/ml
Methylprednisolone Na Succinate Preservative Free Ophthalmic Solution $77.95/10m
Prednisolone Acetate Preservative Free Ophthalmic Suspension $92.75/10ml
Prednisolone Sod Phos Preservative Free Ophthalmic Solution $82.90/10ml
Rimexolone 0.5% Cmpd PF ** Ophthalmic Solution $102.60/10ml
Triamcinolone 80mg/ml Preservative Free Compound Injection $20.00/1ml
Misc. Agents
Acetyl Cysteine 5-20% Ophthalmic Solution pf $77.95-97.70/10ml
Aminocaproic Acid 30% Ophthalmic Suspension $85.85/10m
Ascorbic Acid 10% Ophthalmic Suspension $87.85/10ml
Bevacizumab (Avastin) Cmpd Inj (various doses available) varies
Bevacizumab (Avastin) Topical Drops varies
Benoxinate 0.4% PF or Preserved Oph Solution $32.06/5ml
Boric Acid Ophthalmic Ointment $82.90/4gm
Brilliant Green 2% Ophthalmic Stain $32.06/10ml
Brilliant Blue G 0.25mg/1ml $10.00/1ml
Cysteamine 0.55% Cmpd Ophthalmic Solution $83.90/10ml
Diclofenac Sodium 0.1% Preservative Free Ophthalmic Solution $77.95/10ml
EDTA Preserved 0.4% to 3% varies
Ethanol (all concentrations) Ophthalmic Drops or Injectable $53.30/10ml
Indomethacin 0.5 or 1% Ophthalmic Suspension $92.75/15ml
Glutathione 6% Ophthalmic Solution $59.50/15ml
Glycerin 50% oral solution $55.60/220ml
Glycerin 50% Ophthalmic Solution $30.53/10ml
Guanethidine Preservative Free Ophthalmic Solution 2%, 5% or 7.5% varies
Heparin PF Ophthalmic Solution $32.06/10ml
Hyaluronidase Injection 150u/ml $15.00/1ml, $31.25/5 ml, $46.25 /10ml
Ibopamine 2% Ophthalmic Solution $65.00/5ml,$85.00/10ml
Interferon Alfa 2B Ophthalmic Solution (1-3mu/ml) $235.73/3-10ml (depends on strength)
Isosorbide 45% Cmpd Oral Solution $128.75/110ml
Medroxyprogesterone Acetate 0.5% or 1% Ophthalmic Suspension $40.91/10ml
PABA 10% Cmpd Ophthalmic Ointment $60.03/4gm
Phentolamine 0.083% Ophthalmic Solution $41.00/5ml
Physostigmine Salicylate 0.03%, 0.125% 0.25% or 0.5% Oph Solution $77.95/10ml
Physostigmine Salicylate Ophthalmic Ointment $87.85/4gm
Povidone-Iodine Ophthalmic Solution $53.30/10ml
Silver Nitrate Ophthalmic 0.5% or 1% Solution $53.30/10ml

Silver Protein 10% Ophthalmic Solution $44.15/10ml
Sodium Chloride 5% Ophthalmic Solution PF $53.30/10ml
Sodium Chloride 5% Preservative Free Ophthalmic Ointment $63.20/4gm
Sodium Citrate 10% Ophthalmic Solution $69.10/10ml
Tetrahydrolazine 0.05% PF Ophthalmic Solution $53.30/10ml
Vision Blue 0.06% Singles $52.00/each
Vitamin A 1%/ Vit C 1% /Glutathione 1%/DMSO 5% Ophthalmic Sol $98.70/10ml

Topical Anesthetics, Reversal Agents and Combo Dilating Agents

Atropine Sulfate Ophthalmic Solution 0.125% to 1% PF $50.90/10ml
Benoxinate 0.4% PF or Preserved Oph Solution $32.06/5ml
Cyclopentolate 0.5% to 1% P.F. $77.95/10ml
Cyclopentolate/Phenylephrine/Bupivicaine Combo Ophthalmic Solution varies
Cyclopentolate/Phenylephrine/Diclofenac Combo Ophthalmic Solution varies
Cyclopentolate/Phenylephrine Combo varies
Cyclopentolate/Proparacaine Combo varies
Dapiprazole 0.5% Topical Drops (compare to Rev-Eyes-Lyopholized) $40.00/6ml kit
Homatropine Preservative Free Ophthalmic Solution 5% $43.45/10ml
Lidocaine Ophthalmic Solution 0.5-0.4% $53.30/10ml
Phenylephrine Preservative Free Ophthalmic Solution 2.5% or 10% $53.30/10ml
Proparacaine Preserved or PF (0.03%, 0.05%, 0.1%, 0.25%) Ophthalmic Solution $43.35/10ml
Proparacaine 0.05% PH Adjusted Preserved Ophthalmic Solution $32.06/10ml
Proparacaine/Tropicamide/Cyclopentolate/Phenylephrine Combo Oph Sol varies
Scopolamine 0.25% Preservative Free Ophthalmic Solution $65.65/10ml
Tetracaine 0.5% PF Cmpd Ophthalmic Solution $32.06/5ml
Tetracaine 0.5% Ophthalmic Ointment $82.90/4gm
Tetracaine HCL 0.05% Preserved and Stabilized Oph Solution (Comfort Drops) $7.50/3 or 5ml
Tropicamide Preservative Free Ophthalmic Solution $53.30/10ml
Tropicamide 0.5%/Cyclopentolate 0.5%/PHN 2.5% Combo Spray $48.30/10ml
Tropicamide 1%/ Cyclopentolate 1% Ophthalmic Solution $53.30/10ml
Tropicamide 1%/ Phenylephrine 2.5% Preserved Ophthalmic Solution $53.30/10ml
Tropicamide 1%/ Phenylephrine 5% Preserved Ophthalmic Solution $53.30/10ml
Tropicamide 0.25%/ Phenylephrine 5% Preserved Ophthalmic Solution $53.30/10ml
Topicamide 1%/Cyclopentolate1%/Phenylephrine 2.5% Preserved Ophthalmic $54.80/10ml

Appendix B: To ensure physicians are able to secure necessary compounded treatments for their patients, ASCRS has compiled this list of bulk drug substances, that should be included on the 503B Bulks List and explanations for their inclusions.

Bulk Drug Substance	Clinical Need Explanation
Azithromycin	The only FDA approved products contain as a preservative, benzalkonium chloride, an agent with known ocular toxicity when used chronically. There are certain clinical situations, such as Meibomian gland dysfunction and episodic dry eye conditions that require the administration of azithromycin for weeks and months at a time. For these patients, it is imperative to provide an alternative without a preservative to treat the conditions and enhance the corneal surface simultaneously. Starting with the bulk substance is necessary to achieve these clinical outcomes.
Brimonidine Tartrate	No preservative-free FDA approved product, therefore it must be compounded from the bulk substance. Preservatives have known ocular surface toxicity when used chronically.
Cyclopentolate - Tropicamide - Phenylephrine - and - Tropicamide - Phenylephrine	While cyclopentolate and phenylephrine are available as FDA approved products in concentrations greater than 1% and 2.5% respectively, tropicamide is only available in 0.5% and 1%. Dilution of the commercially available Tropicamide with the other actives would therefore result in significantly lower concentration of Tropicamide from the required 1 %. The delicate nature of eye dilation is best accomplished with each component maintaining its optimal concentration, and using commercially available products does not allow for this. Further, simply mixing sterile products together does not allow control of critical attributes such as pH of the final mixture. Compounding from bulk drug allows each lot of material to be consistent and comparable to the lot used to establish the Beyond Use Period (BUD) for the outsourced product. The BUD can be affected by pH of the finished product which without compounding is subjected to the vagaries of the pH contribution from the individual commercial products. For example, the allowed pH range for one of the actives can be as great as 3 to 7.5. whereas the compounded CTP is controlled with an in-process pH requirement of 4.5 to 4.8.
Cyclopentolate - Tropicamide - Phenylephrine HCl - Proparacaine HCl	These combination products are necessary to affect pupillary dilation prior to intraocular surgery. The approved FDA products are available individually but in fixed concentrations. It is critically important to use the lowest, most effective concentration to avoid systemic side effects associated with these solutions. Each active ingredient contains a different mechanism of action and work synergistically to produce Mydriasis. Simply combining the FDA approved products would lead to a dilution of each requiring multiple drop administration and potential for systemic side effects and therefore must be compounded from the bulk substances.
Cyclosporine	Clinical literature teaches the use of higher concentrations in individuals with little or no response to the FDA approved concentration in the approved product.

	There are also many patients that cannot tolerate the discomfort and irritation associated with the commercially available drops. In order to accomplish this, it must be compounded from the bulk substance as there is no way to achieve the appropriate concentration (higher) from the commercial product.
Dexamethasone Phosphate - Moxifloxacin HCl - Ketorolac Tromethamine	A preservative-free intraocular injection used after cataract surgery to prevent endophthalmitis and cystoid macular edema, serious complications from intraocular surgery. This is especially important for patients who have physical and mental disabilities and cannot administer drops. The FDA approved products are not prepared in the appropriate concentrations to allow for the very small amount of volume required for injection. And in some cases, the approved products contain preservatives known to be toxic to the eye. There is currently no approved intraocular injection form of ketorolac tromethamine and therefore must be compounded from the bulk substances.
Disodium Edetate	Disodium EDTA has no FDA approved product to use. Disodium EDTA was removed from the marketplace due to concerns providers would confuse it with Calcium EDTA, which historically had happened. Disodium EDTA is a chelating agent used to remove calcium deposits on the eye, band keratopathy.
Dorzolamide HCl	Medical literature shows that preservatives in approved FDA products are toxic to cornea and epithelium. With few exceptions, FDA approved glaucoma medications contain preservatives and hence cannot be used to compound these products. Additionally, combination therapies result in improved compliance for glaucoma patients. Many require 3 and sometimes 4 separate medicines used at different intervals during the day, with 5-20 minutes in between each administration. Making thee combinations without preservatives requires the use of bulk drug substances.
Hyaluronidase	Sodium Hyaluronate is used to improve spreading of anesthetic through orbital soft tissues after retrobulbar injection. The FDA approved hyaluronidase injection is available commercially in strengths that are significantly lower than the necessary concentration used in this procedure. The commercially available products are available in 150 unit/ml or 200 unit/ml concentrations, well below the 300 unit/ml concentration necessary for this procedure and must therefore be compounded from the bulk substance.
Latanoprost	No preservative-free FDA approved product, therefore it must be compounded from the bulk substance. Preservatives have known ocular surface toxicity when used chronically.
Lidocaine HCL - Phenylephrine HCL	Lidocaine HCL is available in a 2% preservative free injectable from FDA approved finished products, but phenylephrine is only available in a 1.0%(10mg/ml) presentation as a FDA approved product, well below the required strength for the required product. Furthermore, the FDA approved 1.0% phenylephrine injection contains sodium metabisulfite, which is an agent with known toxicity to the eye. It is therefore necessary to compound this product from bulk drugs in order to

	achieve the required active strengths and avoid sulfites. Lidocaine HCL 1%/phenylephrine 1.5% is a dilating agent and assists physicians overcome IFIS in certain patients.
Lidocaine/Epinephrine	Lidocaine/epinephrine in BSS PF/SF (0.75/0.0025)%. It is necessary to compound this product from bulk drug substances in order to achieve the required active strengths, avoid preservatives and avoid sulfites. Lidocaine HCL 0.75% and epinephrine 0.0025% is a dilating agent and assists physicians overcome IFIS in certain patients.
Loteprednol	FDA approved loteprednol drops contain a preservative, benzalkonium chloride, an agent with known ocular toxicity when used chronically. There are certain clinical situations, such as Meibomian gland dysfunction and episodic dry eye conditions that require the administration of loteprednol for weeks and months at a time. For these patients, it is imperative to provide an alternative without a preservative to treat the conditions and enhance the corneal surface simultaneously. Loteprednol is available as a FDA approved preservative free gel, however, the gel cannot be converted to drop. Therefore, starting with the bulk substance is necessary.
Mitomycin	Mitomycin is available in a FDA approved presentation as a lyophilized product. However, Mitomycin is extremely labile and its stability dependent on the pH of the solution. FDA approved commercial product is only certified to have a pH between 6.0-8.0. Compounded Mitomycin 0.04% sterile solution is controlled during preparation to a pH of 6.5 to 7.0. This assures a consistent stability and BUD from lot to lot.
Moxifloxacin	Moxifloxacin injection is only available in the market as a 400mg/250ml product. As the compounded product strength is higher than commercially available FDA approved product It is not possible to provide the required ophthalmic product without compounding from bulk drug product. This product can be used to both prevent or treat ophthalmic infections.
Phenylephrine HCl - Lidocaine HCl	Lidocaine HCL is available in a 2% preservative free injectable from FDA approved finished products, but phenylephrine is only available in a 1.0% (10mg/ml) presentation as a FDA approved product, well below the required strength for the required product. Furthermore, the FDA approved 1.0% phenylephrine injection contains sodium metabisulfite, which is an agent with known toxicity to the eye. Therefore, it is necessary to compound this product from bulk drug substances in order to achieve the required active strengths and avoid sulfites. Lidocaine HCL 1%/phenylephrine 1.5% is a dilating agent and assists physicians overcome IFIS in certain patients.
Povidone Iodine - Lidocaine HCl	Treatment of retinal disease with intravitreal injections (IVI) has revolutionized the field of ophthalmology. A very specific and high-risk procedure, considered a subspecialty skill, is associated with discomfort and the risk of infection (endophthalmitis) among others. This combination, not currently available, can

	minimize both risks. The individually FDA approved products would cannot be combined as the yielding solution would be too dilute for intended prophylaxis and therefore must be compounded from the bulk substances.
Prednisolone Acetate - Gatifloxacin - Bromfenac Sodium	These combination products are designed to enhance therapeutic outcomes and patient compliance as prophylaxis against endophthalmitis, inflammation and cystoid macular edema. The individual FDA approved products require multiple different administration schedules and spacing between administration. This has been demonstrated clinically to lead to lack of compliance and higher incidence of complications, especially in patients who are physically and mentally challenged. Simply combining the different approved products would lead to a dilution in concentration which could result in breakthrough inflammation and infection. It is therefore, necessary to compound them from the bulk substance.
Prednisolone Phosphate - Gatifloxacin - Bromfenac Sodium	These combination products are designed to enhance therapeutic outcomes and patient compliance as prophylaxis against endophthalmitis, inflammation and cystoid macular edema. This is especially important for patients who have physical and mental disabilities and cannot administer commercially available drops requiring multiple different administration schedules and spacing between administration. This has been demonstrated clinically to lead to lack of compliance and higher incidence of complications. It is not possible to simply combine the different approved products as this would lead to a dilution in concentration which could result in breakthrough inflammation and infection. It is therefore, necessary to compound them from the bulk substance.
Tacrolimus	There is a body of clinical literature that supports the benefits of Tacrolimus for use in ocular surface disease. There is currently no FDA approved ophthalmic product and therefore must be compounded from the bulk substance.
Timolol Maleate	Medical literature teaches that preservatives in approved FDA products are toxic to cornea and epithelium. With few exceptions, FDA approved glaucoma medications contain preservatives and hence cannot be used to compound these products. Additionally, combination therapies result in improved compliance for glaucoma patients. Many require 3 and sometimes 4 separate medicines used at different intervals during the day, with 5-20 minutes in between each administration. Making thee combinations without preservatives requires the use of bulk drug substances.
Tobramycin	Infectious keratitis if not treated with high concentration antibiotics, can lead to scarring of the cornea and blindness. The concentrations required are much higher than the commercially available Tobramycin eye drops that are FDA approved. It is necessary to compound these solutions using the bulk substance to achieve the appropriate concentrations.
Triamcinolone Acetonide - Moxifloxacin HCl	A preservative-free intraocular injection used after cataract surgery to prevent endophthalmitis and inflammation which can be serious complications from intraocular surgery. This is especially important for patients who have physical

	and mental disabilities and cannot administer drops. The FDA approved products are not prepared in the appropriate concentrations to allow for the very small amount of volume required for injection. And in some cases, the approved products contain preservatives known to be toxic to the eye. There is currently no approved intraocular injection form of moxifloxacin and therefore the injection must be compounded from bulk substances.
Vancomycin	Infectious keratitis if not treated with high concentration antibiotics, can lead to scarring of the cornea and blindness. There is currently no FDA approved Vancomycin ophthalmic solution, so it is necessary to compound these solutions using the bulk substance to achieve the appropriate concentrations.