October 5, 2018

Julie Dohm, JD, PhD
Senior Science Advisor for Compounding
Center for Drug Evaluation & Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Dohm,

On behalf of the undersigned organizations, we would like to thank you again for meeting with us on April 30, 2018, to discuss our concerns with the implementation of the compounding provisions of the Drug Quality and Security Act (DQSA) and its impact on the availability of compounded drug products. We also appreciate the opportunity to participate in the recent FDA compounding listening session, where we expressed concerns that the FDA's recent draft guidance, "Evaluation of Bulk Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act," would impede access to many important compounded drugs in ophthalmology. In response, you requested a list of bulk drug substances that ophthalmologists depend on to care for patients. Attached to this letter, please find a list of these important bulk drug substances and scientific literature to support their inclusion on the 503B Bulks Drug List for compounding in outsourcing facilities. **We urge the FDA to include all bulk drug substances on this list to ensure patients and physicians have access to necessary compounded drugs to treat ocular conditions**.

We support FDA actions that ensure the safety of compounded drugs; however, we remain concerned that the proposal to limit compounding from bulk drug substances will limit access to necessary ophthalmic drugs from 503B outsourcing facilities and will harm patients. Many FDA-approved drug products do not have the same strength, routes of administration, or formulation needed to treat ocular disease. Furthermore, most FDA-approved drugs contain preservatives to prevent microbial contamination. These preservatives may cause significant adverse reactions (cell damage, inflammation, scarring, allergy) in a small subset of patients, making it necessary for ophthalmologists to prescribe preservative-free compounded medications for these patients. This may occur with short-term use, but the risk is increased if a drug is being used long-term. Therefore, **we urge the FDA to recognize that there are frequent circumstances in ophthalmology in which it is not appropriate to compound from drug substances that are components of FDA-approved drug products, necessitating the use of the bulk substances on the attached list.**

Additionally, the FDA regulates outsourcing facilities and the quality of its compounded drugs using stringent requirements, including the Current Good Manufacturing Practice (CGMP) to ensure patient safety. Outsourcing facilities must perform quality control tests on each drug ingredient they use. Furthermore, outsourcing facilities follow strict purchasing guidelines, mandating procurement of bulk

drug substances directly from a manufacturer regulated by the FDA. According to the FDA, 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 and increases the difficulties associated with compounding by CGMP facilities, as it restricts their ability to compound. **We urge the FDA not to limit physician and patient access to drugs being compounded in 503B outsourcing facilities that have a higher assurance of safety.**

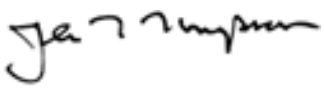
We encourage the FDA to recognize the necessity and importance of bulk drug substances when compounding ophthalmic drugs. If 503B outsourcing facilities are unable to use the most appropriate bulk drug substance for compounding, then patients' treatment options will be limited. Therefore, it is essential that the drugs we identified are included on the 503B Bulks List for compounding in outsourcing facilities. We encourage the FDA not to limit physician and patient access to drugs produced in facilities with federal oversight that offer greater assurance of quality.

Our organizations appreciate your efforts to implement the Drug Quality & Security Act, and we look forward to future engagement on these important issues. Should you have any questions or wish to schedule a meeting with our organizations, please contact Allison Madson, American Society of Cataract and Refractive Surgery, at amadson@ascrs.org or 703-291-2220, or Scott Haber, American Academy of Ophthalmology, at shaber@aao.org or 202-737-6662.

Sincerely,

Parag Parekh, MD, MPA
Chairman, Government Relations Committee
American Society for Cataract and Refractive Surgery

David Glasser, MD
Secretary of Federal Affairs
American Academy of Ophthalmology



John T. Thompson, MD
Health Policy Chair
American Society of Retina Specialists

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

Drug Name: **Acyclovir**
Ophthalmic Use: Viral infections of the retina
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 200 mcg / 0.1 mL
Route of Administration: Intravitreal

Reason for placement on 503B Bulks List: FDA-approved version for intravenous use has a pH between 10.7 and 11.7, which is toxic to the retina. A neutral-pH version for intravitreal injection must be compounded from the bulk substance.

Drug Name: **Azithromycin**
Ophthalmic Use: Meibomian gland dysfunction, chronic ocular surface disease
Approved product for this ophthalmic condition? Yes
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 10 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: "Off-label chronic topical application of azithromycin, typically in a pulsed fashion (once daily for 3 days every 2-4 weeks) is used with success in a small subset of patients with meibomian gland disease refractory to treatment with other topical medications, local mechanical therapy and/or systemic antibiotics. A further subset of these patients has significant ocular surface disease with corneal epithelial staining that is aggravated by treatment with any preservative-containing topical drops due to epithelial toxicity. This can occur in isolated cases even with newer preservatives that are less toxic than benzalkonium chloride (BAK).

Specific supporting literature for this indication is sparse because there are not many patients who need these drugs. Those that do, really need them to improve the health of the corneal epithelium. There is well-documented evidence for the toxic effects on the corneal epithelium of preservatives in eye drops contributing to the ocular surface disease associated with tear dysfunction. This is well-summarized with citations to supporting literature in the TFOS DEWS II Iatrogenic Report, Section 4.2, Topical drug-induced DED. Specifics regarding preservatives are discussed in Section 4.2.3.1, Role of preservatives and excipients. [Gomez JAP, et al. TFOS DEWS II Iatrogenic Report. The Ocular Surface 2017;15:511-538.] For this small cohort of patients and the even smaller cohort that may demonstrate preservative sensitivity, a preservative-free version of the drug may be the only available treatment which will be tolerated. The preservative-free version must be compounded from the bulk substance.

There are valid concerns about contamination of multi-dose bottles of non-preserved medications, particularly in patients at greater risk of infection due to compromised epithelium. Nevertheless, some clinicians do use these in multi-dose containers. We are not aware of published evidence of an increased risk of infections specifically related to the non-preserved medications in these cases, perhaps because: (1) Patients tend to be followed very closely when staining is significant and infection risk is greatest, typically weekly or more often, (2) Quantities in the containers tend to be

small, typically a week's worth, (3) The need may be temporary, with approved/preserved medications reinstituted and better tolerated once the epithelium has healed and the ocular surface addressed via other modalities. Patients may also be placed on topical antibiotics (e.g. preservative-free moxifloxacin) until the epithelium heals.

Unit-dose containers would eliminate the contamination concern but might be costly/unwieldy. However, unit-doses would be better than not having any access to preservative-free drug. A unit-dose restriction would be acceptable if that is the only way to get this drug on the bulks list. Another option might be to allow multi-dose if a preservative is included. Use of a bulk substance would be necessary to allow compounding with a preservative that is less toxic than BAK."

Drug Name: **Brimonidine tartrate**
Ophthalmic Use: Glaucoma, ocular hypertension
Approved product for this ophthalmic condition? Yes
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 1-2 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: "Brimonidine is a commonly-used topical agent for treatment of glaucoma and ocular hypertension. It is used chronically, typically twice a day. The approved products contain preservatives. A small number of patients with ocular surface disease with corneal epithelial staining, often due to tear dysfunction, will show significant improvement in their corneal staining and visual acuity when switched to the same agent compounded without preservatives.

The lack of published reports showing improvement is due to the small number of patients involved. This can occur in isolated cases even with newer preservatives that are less toxic than benzalkonium chloride (BAK). There is well-documented evidence for the toxic effects on the corneal epithelium of preservatives in eye drops contributing to the ocular surface disease associated with tear dysfunction. This is well-summarized with citations to supporting literature in the TFOS DEWS II Iatrogenic Report, Section 4.2, Topical drug-induced DED. Specifics regarding preservatives are discussed in Section 4.2.3.1, Role of preservatives and excipients. [Gomez JAP, et al. TFOS DEWS II Iatrogenic Report. The Ocular Surface 2017;15:511-538.] For this small cohort of patients and the even smaller cohort that may demonstrate preservative sensitivity, a preservative-free version of the drug may be the only available treatment which will be tolerated. The preservative-free version must be compounded from the bulk substance. While Iopidine (apraclonidine 0.5%) is a preservative-free commercially available alpha-adrenergic intraocular pressure lowering agent, frequent tachyphylaxis, unit dose packaging, and cost make it an unsuitable alternative for chronic therapy.

There are valid concerns about contamination of multi-dose bottles of non-preserved medications, particularly in patients at greater risk of infection due to compromised epithelium. Nevertheless, some clinicians do use these in multi-dose containers. We are not aware of published evidence of an increased risk of infections specifically related to the non-preserved medications in these cases, perhaps because: (1) Patients tend to be followed very closely when staining is significant and infection risk is greatest, typically weekly or more often, (2) Quantities in the containers tend to be small, typically a week's worth, (3) The need may be temporary, with approved/preserved medications reinstituted and better tolerated once the epithelium has healed and the ocular surface

addressed via other modalities. Patients may also be placed on topical antibiotics (e.g. preservative-free moxifloxacin) until the epithelium heals.

Unit-dose containers would eliminate the contamination concern but might be costly/unwieldy. However, unit-doses would be better than not having any access to preservative-free drug. A unit-dose restriction would be acceptable if that is the only way to get this drug on the bulks list. Another option might be to allow multi-dose if a preservative is included. Use of a bulk substance would be necessary to allow compounding with a preservative that is less toxic than BAK."

Drug Name: **Cyclopentolate**
Ophthalmic Use: Cycloplegia for pain control in chronic uveitis
Approved product for this ophthalmic condition? Yes
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 5-20 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: "While chronic use of cyclopentolate for chronic uveitis is extremely uncommon, some of these patients also have corneal epithelial staining or neurotrophic keratitis (e.g. post-zoster), where the corneal epithelium is particularly susceptible to preservative toxicity. These patients may show improvement in corneal staining and visual acuity when switched to a preservative-free agent.

The lack of published reports showing improvement is due to the extremely small number of patients involved. There is well-documented evidence for the toxic effects on the corneal epithelium of preservatives in eye drops contributing to the ocular surface disease associated with tear dysfunction. This is well-summarized with citations to supporting literature in the TFOS DEWS II Iatrogenic Report, Section 4.2, Topical drug-induced DED. Specifics regarding preservatives are discussed in Section 4.2.3.1, Role of preservatives and excipients. [Gomez JAP, et al. TFOS DEWS II Iatrogenic Report. The Ocular Surface 2017;15:511-538.] For this small cohort of patients and the even smaller cohort that may demonstrate preservative sensitivity, a preservative-free version of the drug may be the only available treatment which will be tolerated. The preservative-free version must be compounded from the bulk substance.

There are valid concerns about contamination of multi-dose bottles of non-preserved medications, particularly in patients at greater risk of infection due to compromised epithelium. Nevertheless, some clinicians do use these in multi-dose containers. We are not aware of published evidence of an increased risk of infections specifically related to the non-preserved medications in these cases, perhaps because: (1) Patients tend to be followed very closely when staining is significant and infection risk is greatest, typically weekly or more often, (2) Quantities in the containers tend to be small, typically a week's worth, (3) The need may be temporary, with approved/preserved medications reinstituted and better tolerated once the epithelium has healed and the ocular surface addressed via other modalities. Patients may also be placed on topical antibiotics (e.g. preservative-free moxifloxacin) until the epithelium heals.

Unit-dose containers would eliminate the contamination concern but might be costly/unwieldy. However, unit-doses would be better than not having any access to preservative-free drug. A unit-dose restriction would be acceptable if that is the only way to get this drug on the bulks list. Another option might be to allow multi-dose if a preservative is included. Use of a bulk substance would be

necessary to allow compounding with a preservative that is less toxic than benzalkonium chloride (BAK)."

Drug Name: **Cyclosporine**
Ophthalmic Use: Inflammation - corneal, intraocular; prophylaxis of corneal graft rejection
Approved product for this ophthalmic condition? Yes
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 10-20 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: "The efficacy of topical cyclosporine A (CsA) in preventing graft rejection is controversial. [Abudou M. Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty. Cochrane Database Syst Rev 2015;8].

CsA, particularly in concentrations of 10-20 mg/ml, has been shown in a number of clinical studies to prolong graft survival in high-risk keratoplasty. Ultimate long-term survival rates have been prolonged in some studies but not in others. Some studies have shown no effect on graft survival regardless of risk status. Prospective studies have not shown CsA to be effective in treating established graft rejection. [Belin MW. Topical cyclosporine in high-risk corneal transplants. Ophthalmology 1989;96:1144]; [Belin MW. Update on topical cyclosporin A. Background, immunology, and pharmacology. Cornea 1990;9:184]; [Bouchard CS. The high-risk keratoplasty patient–quo vadis? Cornea 1994;13:1]; [Cosar CB. Topical cyclosporine in pediatric keratoplasty. Eye Contact Lens 2003;29:103]; [Holland EJ. Topical cyclosporin A in the treatment of anterior segment inflammatory disease. Cornea. 1993;12:413]; [Inoue K. Long-term outcome of systemic cyclosporine treatment following penetrating keratoplasty. Jpn J Ophthalmol. 2001;45:378]; [Javadi MA. Efficacy of topical ciclosporin A for treatment and prevention of graft rejection in corneal grafts with previous rejection episodes. Br J Ophthalmol 2010;94:1464]; [Perry HD. Topical cyclosporin A in the management of postkeratoplasty glaucoma. Cornea 1997;16:284]; [Price MO. Efficacy of topical cyclosporine 0.05% for prevention of cornea transplant rejection episodes. Ophthalmology 2006;113:1785]; [Randleman JB. Prevention and treatment of corneal graft rejection: current practice patterns (2004) Cornea 2006;25:286]; [Unal M. Evaluation of topical ciclosporin 0.05% for prevention of rejection in high-risk corneal grafts. Br J Ophthalmol 2008;92:1411]; [Zhao JC. Local therapy of corneal allograft rejection with cyclosporine. Am J Ophthalmol 1995;119:189]. However, CsA and topical corticosteroids have been shown to have an additive effect in preventing graft rejection. [Goichot-Bonnat L. CsA eyedrops in the prevention of high-risk corneal graft rejection. II. Postoperative clinical results. J Fr Ophthalmol. 1987;10:213].

Clinicians are clearly aware of a subset of high-risk keratoplasty patients who can benefit from significantly higher CsA concentrations (10-20 mg/ml) than those that are commercially available (0.5 and 0.9 mg/ml) for prevention of graft rejection. Use of topical CsA at 10-20 mg/ml would allow topical corticosteroids to be reduced or discontinued as part of the rejection prophylaxis regiment in patients who develop elevated intraocular pressure or other side effects of topical corticosteroids. [DiZazzo A. Management of high-risk corneal transplantation. Surv Ophthalmol 2017;62:816]; [Jabbehdari S. Update on the management of high-risk penetrating keratoplasty. Curr Ophthalmol Rep 2017;5:38].

Since approved versions of cyclosporine are well below the concentration needed for this indication (10-20 mg/ml), the drug would need to be compounded from bulk substance."

Drug Name: **Dexamethasone**
Ophthalmic Use: Intraocular inflammation, cystoid macular edema
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 0.4 mg/0.1 ml
Route of Administration: Intravitreal

Reason for placement on the 503B Bulks List: The FDA-approved products for intraocular use (Triesence, Ozurdex, Iluvien) contain longer-acting agents that may be contraindicated in individuals with elevated intraocular pressure (IOP) or a history of IOP elevation associated with corticosteroid use. These patients would benefit from shorter-acting preservative-free dexamethasone. The lack of published reports is related to the small numbers of patients who need short-acting intraocular corticosteroids. The approved topical dexamethasone products contain preservatives that are toxic to intraocular structures, necessitating compounding from bulk substance.

Drug Name: **Disodium EDTA**
Ophthalmic Use: Removal of band keratopathy (calcium chelation)
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 20-100 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: No approved product.

Drug Name: **Glycerol**
Ophthalmic Use: Temporary treatment of corneal edema during examination or intraocular surgery
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 50-75%
Route of Administration: Topical

Reason for placement on the 503B Bulks List: No approved product.

Drug Name: **Phenylephrine**
Ophthalmic Use: Pupil dilation during intraocular surgery, particularly in cases of intraocular floppy iris syndrome (IFIS)
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 15 mg/ml
Route of Administration: Intraocular

Reason for placement on the 503B Bulks List: "Intracameral phenylephrine in a concentration of 15 mg/ml has been shown to be an effective treatment for intraoperative floppy iris syndrome (IFIS) during cataract surgery, allowing surgery to be completed safely in most cases without the need for more invasive mechanical pupil dilation maneuvers. [Lorente R. Prophylaxis against intraoperative floppy iris syndrome: prospective, randomized, fellow eye study. Ophthalmology 2102;119:2053].

The most commonly used intracameral agent for pupil dilation, epinephrine, is typically used by diluting a 1/1000 concentration of the drug in a 500 ml bottle of irrigating solution. The resulting concentration facilitates pupil dilation during routine cataract surgery but is not effective in cases of IFIS. Higher concentrations of epinephrine (e.g. 1/1000 diluted five to ten times) directly injected into the anterior chamber are effective in some cases of IFIS but are not as reliable as phenylephrine 15 mg/ml. This may be due to the degradation of epinephrine that is prepared a few hours prior to surgery.

Phenylephrine is more stable than epinephrine and is not subject to degradation in the typical time frame between compounding and use. The desired phenylephrine concentration for intraocular use (15 mg/ml) is higher than that available in the products approved for topical use. Additionally, approved topical versions of phenylephrine, as well as approved injectable versions of phenylephrine at a concentration of 10 mg/ml, contain sodium metabisulfite, which is toxic to the corneal endothelium.

Phenylephrine hydrochorlide in a concentration of 12.4 mg/ml without metabisulfite is available in Omidria, a product approved for intraocular use to maintain pupillary dilation during cataract surgery. This product was approved based on use in routine cataract surgery. Its efficacy in treatment of IFIS has not been evaluated. Omidria is diluted in 500 ml of irrigating solution for intraocular use, producing a much lower concentration in the eye. It also contains ketorolac tromethamine at 4.24 mg/ml, which is not necessary for maintenance of pupil dilation in IFIS cases when adequate concentrations of phenylephrine are placed into the anterior chamber. Placing undiluted Omidria into the eye in order to achieve adequate phenylephrine concentrations risks toxicity from the undiluted ketorolac and is contraindicated in patients with allergies to nonsteroidal anti-inflammatory agents.

Because there is no approved product from which preservative-free phenylephrine for injection into the anterior chamber at a concentration of 15 mg/ml can be prepared, it needs to be compounded from bulk substance."

Drug Name: **Polyhexamethyl biguanide**
Ophthalmic Use: Acanthamoeba keratitis
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? No
Dosage or Concentration: 0.2-0.8 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: No approved product.

Drug Name: **Prednisolone acetate and Prednisolone phosphate**
Ophthalmic Use: Inflammation - corneal, intraocular
Approved product for this ophthalmic condition? Yes
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 10 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: "Prednisolone phosphate and acetate are mainstays of topical therapy for ocular inflammation. A number of patients require long-term therapy. A small number of these patients with ocular surface disease with corneal epithelial staining, often due to

tear dysfunction, will show significant improvement in their corneal staining and visual acuity when switched to the same agent compounded without preservatives.

The lack of published reports showing improvement is due to the small number of patients involved. This can occur in isolated cases even with newer preservatives that are less toxic than benzalkonium chloride (BAK). There is well-documented evidence for the toxic effects on the corneal epithelium of preservatives in eye drops contributing to the ocular surface disease associated with tear dysfunction. This is well-summarized with citations to supporting literature in the TFOS DEWS II Iatrogenic Report, Section 4.2, Topical drug-induced DED. Specifics regarding preservatives are discussed in Section 4.2.3.1, Role of preservatives and excipients. [Gomez JAP, et al. TFOS DEWS II Iatrogenic Report. The Ocular Surface 2017;15:511-538.] For this small cohort of patients and the even smaller cohort that may demonstrate preservative sensitivity, a preservative-free version of the drug may be the only available treatment which will be tolerated. The preservative-free version must be compounded from the bulk substance.

There are valid concerns about contamination of multi-dose bottles of non-preserved medications, particularly in patients at greater risk of infection due to compromised epithelium. Nevertheless, some clinicians do use these in multi-dose containers. We are not aware of published evidence of an increased risk of infections specifically related to the non-preserved medications in these cases, perhaps because: (1) Patients tend to be followed very closely when staining is significant and infection risk is greatest, typically weekly or more often, (2) Quantities in the containers tend to be small, typically a week's worth, (3) The need may be temporary, with approved/preserved medications reinstituted and better tolerated once the epithelium has healed and the ocular surface addressed via other modalities. Patients may also be placed on topical antibiotics (e.g. preservative-free moxifloxacin) until the epithelium heals.

Unit-dose containers would eliminate the contamination concern but might be costly/unwieldy. However, unit-doses would be better than not having any access to preservative-free drug. A unit-dose restriction would be acceptable if that is the only way to get this drug on the bulks list. Another option might be to allow multi-dose if a preservative is included. Use of a bulk substance would be necessary to allow compounding with a preservative that is less toxic than BAK."

Drug Name: **Tacrolimus**
Ophthalmic Use: Chronic blepharitis, blepharconjunctivitis
Approved product for this ophthalmic condition? No
Does this drug have an FDA-approved product for any indication? Yes
Dosage or Concentration: 0.3-1 mg/ml
Route of Administration: Topical

Reason for placement on the 503B Bulks List: Approval is for atopic dermatitis only. The approved product is difficult to apply to the ocular surface and stings, making some patients intolerant of it. A better-tolerated formulation can be compounded from the bulk substance.