AMERICAN ACADEMY™
OF OPHTHALMOLOGY

20 F Street NW
Suite 400
Washington DC
20001-6701

P.O. Box 7424
San Francisco, CA
94120-7424

T: +1 202.737.6662
www.aao.org

Statement for the Record

George Williams, MD

American Academy of Ophthalmology

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Hearing

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Chairman Burgess, Ranking Member Green, and members of the Committee, I am honored to be testifying before you on behalf of the American Academy of Ophthalmology on a topic critical to the practice of ophthalmology. My name is George Williams, MD, and I am a practicing retina specialist from Michigan. I am also the immediate past Secretary for Federal Affairs and current President-elect for the Academy. As the world's largest association of eye physicians and surgeons, the Academy seeks to protect sight and empower lives by setting the standards for ophthalmic education and advocating for our patients and the public.

Background:

Compounded drugs play a vital role in the treatment of patients across medical specialties, including ophthalmology, dermatology, allergy and immunology, otorhinolaryngology, and others. Ophthalmology is a unique specialty that uses drug dosage forms not commonly used in other areas of medicine. These dosage forms include ophthalmic topical solutions, suspensions, ointments, and treatments that are injected into the eye. In addition, many drugs that are critical to the treatment of ophthalmology patients must be compounded or repackaged for concentration or dosage size, as drug manufacturers do not always make products appropriate for use in the eye. The use of compounded drugs is essential to the treatment of several ophthalmological conditions, including age-related macular degeneration, neovascular glaucoma, infectious endophthalmitis, bacterial corneal ulcers, and other potentially blinding infections and diseases. Compounded pharmaceuticals are also used in surgical settings, as well as for diagnostic office procedures.

Because of the frequent need for these treatments, ophthalmologists rely heavily on access to drugs for "office use" which is the provision and administration of a drug to a patient in the physician's office or other treatment setting without a patient-specific prescription. Having access to drugs for "office use" enables ophthalmologists to have these treatments readily available should patients arrive at the office in need of emergent care due to conditions such as severe infections. A delay in treatment, even by a few hours, can result in permanent vision loss. In other cases, such as the treatment of age-related macular degeneration (AMD), ophthalmologists need to have drugs on hand because they do not know whether a patient will need treatment until an examination can be performed.

The Academy actively engaged with Congress as it sought to create a new oversight structure for compounding pharmacies following the debacle with the New England

Compounding Center. Since the passage of the Drug Quality and Security Act (DQSA), the Academy has been working with ophthalmic subspecialty organizations to ensure continued access to compounded and repackaged drug products for ophthalmology. The Academy and other physician organizations have also tried to engage with the Food and Drug Administration as it has worked to implement the DQSA to maintain access to the treatments that our physicians, and more importantly, their patients need. Despite years of effort, we continue to hear from our members about difficulties they have accessing important compounded drugs. Therefore, this issue remains a critical priority for the Academy and we appreciate the opportunity to share our perspective on DQSA implementation efforts.

Repackaged Biologics:

The Academy has been a vocal advocate for policy that ensures access to all three, current vascular endothelial growth factor (VEGF) inhibitor treatments used by ophthalmologists in the treatment of our patients. This includes the FDA-approved anti-VEGF treatments ranibizumab and aflibercept, as well as repackaged bevacizumab. Availability of these products is critical to patients facing sight-threatening eye disease. We know that individual patients respond differently and may have better outcomes with one treatment versus another.

Since 2005, repackaged bevacizumab (Avastin) has been an essential treatment option for various blinding eye conditions such AMD, diabetic retinopathy, central retinal vein occlusion, neovascular glaucoma, and others. Its use in terms of efficacy and safety is supported by rigorous federally-funded evidence-based clinical research. Ophthalmologists have administered millions of repackaged bevacizumab injections to patients. In fact, during

2014 alone, the Academy estimates over four million injections were administered to patients. The Academy is aware of adverse event clusters associated with intravitreal injections of repackaged bevacizumab, including 2013 events in Georgia and 2014 events in Florida. Events like these, along with the passage of DQSA, have led to necessary changes at compounding pharmacies and improvements in the safety of repackaged bevacizumab.

Since the passage of DQSA, the Academy has tracked endophthalmitis rates within 15 days of an injection among patients with AMD who received anti-VEGF treatments, including compounded bevacizumab. The American Academy of Ophthalmology utilized our IRIS® Registry (Intelligent Research in Sight), which is the nation's largest comprehensive eye disease clinical registry, to track adverse events associated with use of these products from January 2013 to June 2016. The data showed no statistically significant difference in adverse events among different anti-VEGF treatments, including repackaged bevacizumab.

While we understand that the FDA does not factor cost considerations into its policy decisions, the potential financial impact of drugs is often an important consideration for patients. The price differential between the two branded products and repackaged bevacizumab is substantial. Patients may be financially unable to afford the co-insurance and deductible payments associated with the branded products. While the average Medicare beneficiary pays $11 (co-payment) for one treatment with repackaged bevacizumab, the same beneficiary would pay approximately $400 (co-payment) per dose of the FDA-approved alternatives. Many of these patients require monthly treatments. Patients who find it difficult to afford the more expensive alternative may have to make the choice to forgo treatment and will eventually lose vision. Currently, some patients lacking financial resources find access to the FDA-approved products through patient assistance

programs set up by the manufacturers. It is unlikely that these programs could handle the increased demand for approved products created by loss of access to bevacizumab.

If ophthalmology were to lose access to repackaged bevacizumab when medically appropriate, it could cost the Medicare program up to $2 billion per year as physicians are forced to use more expensive treatments.

In February 2015, FDA released Draft Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. The Academy expressed grave concerns over the impact of the policies included in the draft guidance on the ophthalmic use of bevacizumab. In its original draft guidance, the FDA proposed a maximum five-day beyond use date (BUD) for repackaged biologics. Traditionally, compounding pharmacies conduct sterility testing on each lot of repackaged bevacizumab for a period of roughly 14 days prior to shipment. The proposed 5-day BUD would have meant the repackaged drug would have expired before it left the facility or it would have required facilities to forego critical sterility testing which our members would have found to be unacceptable. The proposed 5-day BUD would have effectively ended ophthalmology's use of repackaged bevacizumab.

Fortunately, FDA has listened to the concerns raised by the Academy and other ophthalmology subspecialties. In January 2017, the FDA released an updated draft guidance, which created a pathway to a longer BUD for repackaged biologics in accordance with additional sterility testing outlined by the agency. The new guidance represented a step in the right direction and was recently finalized by the agency. While optimistic about the updated policy, it is important that outsourcing facilities have clarity from FDA with respect

to required testing to extend a repackaged biologic's BUD. The Academy will continue to engage with the agency, Congress and compounding facilities to ensure patient and physician access to repackaged bevacizumab is protected.

Prescription Requirement for 503A

The Academy is concerned about continued access to other, non-biologic, compounded drugs for "office-use. The FDA has issued final guidance on office-use that threatens access to compounded drugs for such use by requiring a patient-specific prescription before a compounded drug can be distributed by a traditional compounding pharmacy. We are concerned that policy outlined in the final guidance forces practitioners to rely solely on outsourcing facilities to meet all their needs for office-use drugs.

While we understand that outsourcing facilities can meet much of ophthalmology's needs, we know that the financial costs involved with testing and Current Good Manufacturing Practices (cGMP) compliance is an impediment to the production of all the compounded drugs ophthalmology relies on. These concerns stem directly from conversations with several outsourcing facilities that have conveyed doubts about their ability to prepare certain compounds that aren't traditionally ordered in bulk. Regardless of how critical these drugs are for patients; their business model is not to compound drugs at a financial loss. Facilities have also explained that in instances where they are willing to prepare small batch drugs to meet a given need, physicians and patients alike will face steep costs that may render many drugs unaffordable. The loss of access to these products is exceedingly

problematic, especially if they are used to treat urgent or emergent conditions, as a treatment delay of even a few hours can result in a patient suffering permanent vision loss.

As an example of the unintended consequences of this policy, I would like to share a story from one of our members treating patients in my home state of Michigan.

The patient is a 31-year-old woman who resides in the state of Michigan. She is a soft lens wearer and having developed eye pain, she saw a local provider and given a diagnosis of Herpes simplex keratitis. Initial cultures were negative but over the next week she developed radial perineuritis of her cornea, a sign highly suggestive of Acanthamoeba keratitis. Cultures of her contact lens case grew Acanthamoeba and compounded polyhexamethyl biguanide (PHMB) was prescribed. Unfortunately, the local Michigan pharmacy was not then able to compound PHMB and another source, Leiter's pharmacy in San Jose, CA, could not ship it to Michigan. The Michigan ophthalmologists contacted the University of Illinois at Chicago (UIC) Eye and Ear Infirmary and their cornea fellow talked with their pharmacy, which is very experienced with PHMB compounding. They were willing to supply the drug, but only within Illinois, and only if the patient registered as a UIC patient. The patient, then having extreme light sensitivity and severe pain, was driven from Livonia, Michigan to Chicago, 225 miles each way, by her husband. Fortunately, she responded well to PHMB treatment and regained full vision over the course of three months.

Stories like these are why the Academy has been so vocal on this issue and why we support policy that ensures access to drugs for office-use, such as H.R. 2871, the Preserving Patient Access to Compounded Drugs Act, introduced by Congressman Morgan Griffith. While we adamantly believe that compounded drugs must be manufactured safely and be subject to

critically important testing, there is a point where policy becomes restrictive and in turn negatively impacts a physician's ability to properly and effectively treat our patients. It is also important that we point out that ramifications stemming from access issues are exacerbated in more rural parts of the country.

The Academy, as well as other physician groups, has highlighted availability concerns to FDA both through written comment and during the agency's 2017 listening session with physician stakeholders. In a step towards increasing awareness of drug availability, the FDA recently released a product list of compounded drug products currently being provided by outsourcing facilities. While the Academy appreciates the release and update of the product list, it did not alleviate our previously mentioned concerns as many compounded ophthalmic drugs remain absent from the list.

In addition, I would note that according to the FDA's list, some of the compounded drugs used by ophthalmology are only being made by a single facility. This raises questions regarding the ability of that facility to meet ophthalmology's needs nationwide. We are concerned that dependence on a single facility leaves physicians and patients vulnerable to supply interruptions should that facility's production encounter technical difficulties or is perhaps impacted by a natural disaster. There is also the potential for inflated costs to obtain the drug. Ophthalmology's recent experiences with ophthalmic drugs in the generic market, including rapid price increases and shortages, have made the Academy sensitive to these types of problems.

The Academy hopes to discuss ways to improve future updates of the product list with the agency, including ways to include more real-time information, detailing contact information for facilities, pricing, and other information that would improve awareness and timely acquisition of available products.

Physician In-Office Compounding

The Academy is also concerned about FDA policy that may infringe upon physician in-office activities, including reconstitution of botulinum toxin with an anesthetic. These are low risk activities that have been performed in physician offices for years without increasing odds of adverse events. The FDA, as well as the United States Pharmacopeia, has expressed concern over such activities elevating risks to patients but these concerns are not supported by credible data. In fact, the Academy tracked 91,623 botulinum injections between 2013 and 2016 through its IRIS data registry with only 61 potential adverse events.

While we understand that compounding activities, specifically sterile compounding, should not be undertaken in a physician's office, minor office preparation activities that have been a safe and effective part of patient care should not be considered compounding activities by regulatory bodies. The Academy believes that any efforts to include these activities under the definition of compounding are misguided and will be detrimental to patient care.

Engagement with Physician Community

As DQSA implementation efforts move forward, we urge the FDA to make additional strides in engaging with the physician community and for the agency to be more proactive in finding avenues to incorporate physician perspectives. While the FDA has convened stakeholder "listening sessions," the limited time allocated to those sessions have not always allowed for substantive discussion of the issues of concern to the physician community. It has also been challenging for many stakeholders to engage the FDA in one-on-one discussions. The inability to communicate directly with agency leadership and DQSA implementation staff on these issues has been a major source of frustration for the stakeholder community.

Additionally, given our specialty's heavy reliance on compounded and repackaged drugs, the Academy has been disappointed that an ophthalmologist has not been selected to serve on the FDA's Pharmacy Compounding Advisory Committee (PCAC).

Closing Remarks

Despite serious concerns about implementation policy, we remain tremendously supportive of efforts by Congress and FDA to improve the safety of compounded drug products. As implementation efforts move forward, we would urge a greater emphasis on ensuring policy that promotes patient safety does not do so at the expense of patient access to these vital treatment options.

The Academy stands ready to work with any and all stakeholders on efforts to improve implementation of the law and ensure compounded drugs remain safe and effective treatment options for our patients. On behalf of the Academy and the ophthalmic community, I thank you for your time in allowing me to discuss this critically important issue. I look forward to your questions.