American Society of Retina Specialists (ASRS) Comments
FDA Public Meeting May 21, 2019:
''FDA's Proposed Current Good Manufacturing Practice Policies for Outsourcing Facilities: Considerations Regarding Access to Office Stock''

Thank you for the opportunity to present during this public meeting on the FDA's proposed Current Good Manufacturing practice (CGMP) policies for outsourcing facilities and its impact on access to office stock. On behalf of the American Society of Retina Specialists (ASRS), its members and their patients, we submit the following comments on these issues.

The ASRS is the largest retinal organization in the world, representing over 3,000 members and over 90 percent of retina specialists in the United States. Retina specialists are board certified ophthalmologists who have completed fellowship training in the medical and surgical treatment of retinal diseases. The mission of the ASRS is to provide a collegial and open forum for education, to advance the understanding and treatment of vitreoretinal diseases, and to enhance the ability of its members to provide the highest quality of patient care.

Retina patients are treated with many compounded therapies including injectable antibiotics, anesthetics, dyes used during surgery, and repackaged bevacizumab (Avastin). In general, retina doctors have access to these therapies either through 503B outsourcing facilities, or through 503A facilities pursuant to an individual prescription. However, in certain emergencies we have difficulty obtaining medications needed for our patients.

<u>Limited access to compounded antibiotics for intravitreal injection</u>

Since 2016, when the FDA released its initial draft guidance, "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act," ASRS and other ophthalmology organizations have been expressing concerns related to patient safety and physician access to drugs for office-use. In that draft Guidance, the FDA acknowledged that retina specialists need to have compounded antibiotics on hand to treat emergency infections inside the eye such as endopthalmitis. To quote the draft Guidance it said:

> "[s]ometimes it is necessary for health care practitioners in hospitals, clinics, offices, or other settings to have certain compounded drug products on hand that they can administer to a patient who presents with an immediate need for the compounded drug product. For example, if a patient presents at an ophthalmologist's office with a fungal eye infection, timely administration of a compounded antifungal medication may be critical to preventing vision loss. In such a case, the prescriber [physician] may need to inject the patient with a compounded drug product immediately, rather than writing a prescription and waiting for the drug product to be compounded and shipped to the prescriber [physician]."

Even in a nonemergency situation, the FDA acknowledged that when a compounded drug must be administered by a physician in the office it is preferable for the physician to have the drug in the office to administer immediately upon diagnosis, rather than ordering the drug and having the patient return to the office 1-3 days later for administration.

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We agreed with the FDA. The draft guidance further stated that health care practitioners could obtain these non-patient-specific compounded drug products from outsourcing facilities registered under section 503B. To that point, we disagreed. In comments to the agency and testimony at a 2016 listening session ASRS expressed concern that the requirement to obtain a patient specific prescription would hinder our ability to timely treat patients with antifungal antibiotics for intravitreal use because they were not currently available from a 503B facilities. We explained that ophthalmologists across the country typically obtained antibiotics to treat endophthalmitis via 503A compounders. We urged the FDA to create an exception to the prescription requirement for these and other needed compounded medications by allowing such drugs to be obtained without a patient specific prescription from 503A facilities when they cannot be obtained from 503B facilities. However, despite this plea, the Guidance was made final later that year.

Because the compounded drugs we need for "office stock" are often ordered in small quantities, as they are temporary or only for emergencies, outsourcing facilities do not have the flexibility, nor is it economically feasible for them to compound in small quantities and meet the current good manufacturing practices. We have provided the FDA a list of examples of compounded intravitreal antibiotics, antivirals, and antifungals that are only available through 503A compounding pharmacies. Those drugs include: acyclovir, amikacin, amphotericin, clindamycin, foscarnet, gancyclovir, and voriconazole. While intravitreal vancomycin and ceftazidime are available from 503B facilities for bacterial endophthalmitis, there are no 503B available agents for fungal or viral infections or in the event a patient is allergic to vancomycin or cephalosporins.

The problems we identified in 2016 remain uncorrected. Retina specialists remain unable to obtain such office stock from 503A compounding facilities due to obstacles in FDA policy and we have continued to urge the FDA to create an exception. Last year, the ASRS joined the American Academy of Ophthalmology (AAO) and the American Society for Cataract and Refractive Surgery (ASCRS) in a letter to the FDA explaining that we view 503A compounding pharmacies as critical to filling the treatment gap for our specialty to ensure access to important compounded medications to treat patients with emergent ocular conditions. At a minimum, we strongly urged the FDA to prioritize the needs of patients with emergent diseases such as infection to allow compounding in small quantities for office-use without a patient-specific prescription. Vision loss will result if these bacterial and fungal infections are not treated promptly. **We are here today to again urge the FDA to make a common sense exception to the patient specific requirement when needed compounded medications cannot be obtained from an outsourcing facility.**

<u>Current Good Manufacturing Practice Policies for Outsourcing Facilities</u>

ASRS acknowledges and agrees with the FDA that the CGMP safety and quality standards are important for safety and effectiveness of compounded drugs. Yet the problem remains that we are unable to force 503b facilities to produce small quantities are not cost effective for outsourcing facilities to produce. We thank the FDA for listening to stakeholders and revising its draft CGMP policies to provide more flexibility for outsourcing facilities with respect to stability testing, including assignment of a beyond use date (BUD) as an expiration date, by proposing a clear definition of "in-use time," distinguishing it from BUD and "expiration date," and regarding release testing and collection and use of reserve samples.

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Although we are hopeful that it will lead to more outsourcing facilities and production of a broader scope of ophthalmic drug products for hospitals and physicians, ASRS has received feedback from outsourcing facilities commonly used by retina specialists (Pine, Avella, Leiters) that even with this increased flexibility, the financial costs associated with small batch preparations will remain an obstacle to production. ASRS submitted comments on the revised draft Guidance indicating that, and expressing our continued concern that 503B outsourcing facilities will not be willing to compound drugs in the quantity needed by retina practices for office stock due to such costs.

If the FDA policy continues without an exception, with limited options from 503B facilities, some retina doctors may return to do-it-yourself mixing of antibiotics. Twenty years ago, retina specialists mixed antibiotics in their offices with very little specific training and using techniques that did not even meet the standards of USP 797 to treat endophthalmitis. This would represent a major step backwards in terms of safety as compared to antibiotics and antifungals produced by a 503A facility. ASRS believes an exception must be made to allow physicians to continue to administer critically necessary compounded drugs to patients when such drugs are not available from 503B facilities.

In summary, ASRS continues to urge the FDA to create an exception from its requirement for a patient specific prescription to allow physicians obtain compounded drugs from a traditional compounding pharmacy to keep on hand in the office to use for patients who present with an immediate need or an emergency when such drugs are not available from a 503B facility. We don't believe that outsourcing facilities are going to fill this critical gap in needed drug treatments that only compounding pharmacies are willing to fill.

Thank you again for the opportunity to present our thoughts and concerns on these important issues for our patients.

Respectfully,

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