

American Society of Retina Specialists (ASRS) Statement  
Compounding Listening Session, June 3, 2016  
Food and Drug Administration

Thank you for the opportunity to present during the 2016 listening sessions on drug compounding. On behalf of the American Society of Retina Specialists (ASRS), its members and their patients, we submit the following comments on FDA draft guidance documents. The ASRS is the largest retinal organization in the world, representing over 2700 fellowship-trained members. Retina specialists are board-certified ophthalmologists who have completed fellowship training in the medical and surgical treatment of retinal diseases.

Retina patients are treated with a myriad of compounded therapies including injectable antibiotics, anesthetics, dyes used during surgery, and 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 accessing medications needed for our patients.

### **Limited access to compounded antibiotics for intravitreal injection**

We would like to thank the FDA for acknowledging the need for retina specialists to have compounded antibiotics on hand to treat emergency infections such as endophthalmitis. This scenario is described in the current draft guidance on the prescription requirement under Section 503A (line 103 – 110):

“Sometimes, 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 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.”<sup>i</sup>

We agree with FDA that compounded antibiotics on hand are necessary in the case of fungal endophthalmitis, however there still remains no practical solution. The draft guidance later explains, “Hospitals, clinics, and health care practitioners can obtain non-patient-specific compounded drug products from outsourcing facilities registered under section 503B.”<sup>ii</sup> However, for the example of fungal endophthalmitis, antifungal antibiotics for intravitreal use are not currently available from a 503B facility.

Ophthalmologists across the country usually obtain antibiotics to treat endophthalmitis via 503A compounders. For example, the hospital pharmacy at Phillips Eye Institute in Minneapolis, MN, provides a variety of antibiotics through anticipatory compounding. The compounded drugs are frozen and stored in locked refrigerators at the surgery center, clinic, and sister hospital, to be used in the event of emergency. These antibiotics often go unused, are discarded and replaced at the expense of the hospital since patients with infectious endophthalmitis come in at unpredictable intervals. In 2014, the Minnesota Board of Pharmacy granted Phillips Eye Institute a temporary exemption to the individual prescription requirement for ophthalmic antibiotics, pending guidance from FDA. However, the exemption for ophthalmic antibiotics may soon be withdrawn because the current practice violates provisions in recent FDA draft guidance, because (1) these 503A antibiotics are distributed without a patient-specific prescription,<sup>iii</sup> (2) antibiotics are distributed to these multiple locations, in excess of numbers allowed for 1 month average anticipatory compounding,<sup>iv</sup> and (3) the outpatient surgery center, satellite clinics, and sister hospital within the same hospital system are located

several miles away from the pharmacy.<sup>v</sup> In other words, the draft guidance will hinder our preparedness for emergencies such as fungal endophthalmitis.

Specific examples of compounded intravitreal antibiotics that are only available through 503A compounding pharmacies include acyclovir, amikacin, amphotericin, clindamycin, foscarnet, gancyclovir, and voriconazole (see appendix A). Intravitreal vancomycin and ceftazidime are currently available from 503B facilities for bacterial endophthalmitis, but there are no 503B agents for fungal or viral infections or in the event of a patient cephalosporin allergy. Furthermore, intravitreal antibiotics generally speaking are low-volume products that equate to negative revenue for 503B facilities and they will not necessarily be available in the future.

FDA has argued that 503A products are less safe than those from 503B. However, if FDA restricts non-patient-specific 503A antibiotics for ophthalmic use, in the setting of limited options from 503B, 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 similar to a college chemistry lab in order to treat endophthalmitis. The FDA has discouraged “bedside compounding” and retina specialists would have to compound these medications in their office without availability of hoods and proper diluents. This would represent a major step backwards in terms of safety as compared to antibiotics from 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.

*Recommendation: ASRS recommends that FDA uphold its position in draft guidance on the prescription requirement that certain compounded drug products must be on hand to administer to a patient with an immediate need or emergency, such as fungal endophthalmitis, by allowing office use of compounded drugs obtained without a patient specific prescription from 503A facilities when such drugs cannot be obtained from 503B facilities. We further recommend that the FDA strike from its draft guidance on Hospital and Health System Compounding, the words on lines 213 and 214: “and that are located within a 1 mile radius of the compounding pharmacy”*

### **Streamlining the prescription process for 503A compounded drugs**

In its draft guidance on the prescription requirement, the FDA recommends including the following statement along with a prescription for a compounded medication (line 277-278):

“Per [type of communication] with [name of prescriber] on [date], [name of prescriber] has advised that compounded [name of drug] is necessary for the treatment of [name of patient].”<sup>vi</sup>

Writing and transmitting this sentence for each prescription is time consuming for the physician and staff without enhancing the safety of the medication or the prescription process. Furthermore, the statement should reflect information that is already part of the patient’s electronic or paper record.

*Recommendation: ASRS suggests that FDA not include this recommendation in its final guidance.*

### **Proposed Beyond Use Dates (BUDs) for bevacizumab (Avastin) are too short**

ASRS supports the desire of FDA to develop guidelines for compounding and shares its overall goal of decreasing the risk of mass casualties and patient harm. However, we remain concerned that the proposed BUDs for biologics (1 day for 503A facilities, 5 days for 503B facilities)<sup>vii</sup> are prohibitively restrictive and do not recognize overwhelming evidence that Avastin can be repackaged safely with BUDs that are significantly longer. We explained this concern at last year’s listening session and in comments letters to FDA. We are raising the topic again because the guidance on repackaging biologics remains in draft form, and because there

are 3 new publications that support longer BUD for bevacizumab. We hope FDA will consider these new publications before guidance is finalized.

The current standard BUD for prepared syringes of bevacizumab is 3 months or 6 months, with no discernable difference in safety between the two.

Since the listening session last year, Vanderbeek and colleagues published a review of 530,382 intravitreal injections between 2005 and 2012 from the medical claims data of a national medical carrier and found excellent safety for repackaged bevacizumab.<sup>viii</sup> The endophthalmitis rate was 0.017% after bevacizumab as compared to 0.025% for ranibizumab (Lucentis), the FDA-approved non-compounded alternative. Also, Reyes and colleagues published a retrospective series of 503,890 injections of anti-VEGF therapy in a multicenter retrospective study from 5 different geographic locations across the US and also found that the infection rate after injection of repackaged bevacizumab was low and no different from the infection rate after injections of FDA-approved alternative therapies.<sup>ix</sup>

Also, the New England Journal of Medicine published a major prospective multi-center clinical trial evaluating the safety and efficacy of bevacizumab vs. ranibizumab vs. aflibercept in the treatment of diabetic retinopathy.<sup>x</sup> In that trial, a university-based compounding pharmacy successfully extended the BUD for repackaged bevacizumab out to 2 years, based on sterility and stability testing, under the guidance and approval of the FDA.

*Recommendation: We strongly recommend that FDA guidelines allow for scientific evidence and product-specific testing to be used in the determination of maximum BUD for repackaged biologics.*

Thank you again for the opportunity to present our thoughts and concerns on draft guidance documents related to compounding drugs.

Respectfully,

Geoff Emerson, MD, PhD  
Board member  
American Society of Retina Specialists

---

<sup>i</sup> “Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act.” Draft Guidance for Industry. Food and Drug Administration (2016). Lines 103-110.

<sup>ii</sup> Lines 375-377.

<sup>iii</sup> Line 155.

<sup>iv</sup> Line 324-331.

<sup>v</sup> Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act.” Draft Guidance for Industry. Food and Drug Administration (2016). Lines 212-214.

<sup>vi</sup> “Prescription Requirement ...” Food and Drug Administration (2016). Lines 277-278.

<sup>vii</sup> Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. Draft Guidance for Industry (2015). Lines 320-359.

<sup>viii</sup> VanderBeek BL, Bonaffini SG, and Ma L. Association of Compounded Bevacizumab With Postinjection Endophthalmitis. *JAMA Ophthalmol.* 2015;133(10):1159-1164

<sup>ix</sup> Rayes N, Rahimy E, Storey P, Shah CP, Wolfe JD, Chen E, Decroos FC, Garg SJ, and Hsu J. Postinjection Endophthalmitis Rates and Characteristics Following Intravitreal Bevacizumab, Ranibizumab, and Aflibercept. *Am J Ophthalmol* 2016;165:88-93.

<sup>x</sup> The Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med* 2015; 372:1193-1203.

Appendix A

<b>Appendix A: Intravitreal Antibiotics for Endophthalmitis Available from 503B Facilities</b>							
	<b>Advanced</b>	<b>Avella</b>	<b>California</b>	<b>JBC Labs</b>	<b>KRS Global</b>	<b>Leiter's</b>	<b>Pine</b>
<b>Vancomycin</b>	Vancomycin		Vancomycin	Vancomycin		Vancomycin	Vancomycin
<b>Cephalosporin</b>		Cefuroxime	Ceftazidime	Cefuroxime		Cefuroxime	Vancomycin Ceftaz, Cefurox
<b>Amikacin</b>		Amikacin					
<b>Moxifloxacin</b>				Moxifloxacin	Moxifloxacin	Moxifloxacin	Moxifloxacin
<b>Amphotericin</b>							
<b>Voriconazole</b>							
<b>Acyclovir</b>							
<b>Foscarnet</b>							
<b>Gancyclovir</b>							