

May 19, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-1525; Draft Guidance on Mixing, Diluting or Repackaging
Biological Products Outside the Scope of an Approved Biologics License Application

To Whom It May Concern:

The American Society of Retina Specialists (ASRS) welcomes the opportunity to comment on the Draft Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. Specifically, we offer comments on the proposed beyond use dates (BUDs) and how the draft guidance on repackaging biological products impacts access to bevacizumab (Avastin), a sight-saving treatment for age related macular degeneration (AMD) and other serious eye conditions.

The ASRS is the largest retinal organization in the world, representing over 2,750 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.

The ASRS agrees with the Food and Drug Administration's (FDA) overarching goal of establishing regulations that will ensure the safety and effectiveness of repackaged biological products and protect against "contamination and degradation."ⁱ We applaud the FDA and Congress for creating the new category of outsourcing facilities and we fully support requirements that assure that these new facilities meet stringent safety and quality standards, in line with those imposed on drug manufacturing facilities, and that they pass FDA inspections.

The ASRS is also pleased that the FDA is permitting the repackaging of biologic products and has specifically acknowledged that the guidance "could be satisfied even if Avastin is repackaged in multiple single dose syringes."ⁱⁱⁱ While we appreciate the Agency offering Avastin (bevacizumab) as an example of a biologic that could be repackaged into multiple single dose syringes, we are concerned that the excessively short proposed BUDs (4 hours, 24 hours, and 5 days) will effectively prohibit the repackaging of bevacizumab for ophthalmic use.

To remedy this situation, the ASRS encourages the FDA to allow outsourcing facilities to conduct

product specific stability tests to extend the BUD beyond the default, allowing the BUD to be established on a case-by-case basis for each biologic based on the scientific evidence.

BACKGROUND

Anti-VEGFs Used to Treat Eye Diseases

Bevacizumab is a 149-kD humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF-A), a signal protein that stimulates angiogenesis and vasculogenesis in AMD. While bevacizumab received FDA approval for use in the management of various cancers, compounded bevacizumab has been used off label in the treatment of ophthalmic conditions including AMD since May 2005. Today, bevacizumab is successfully used to also treat diabetic retinopathy, central retinal vein occlusion, neovascular glaucoma, and retinopathy of prematurity, in addition to a host of other less common eye diseases.

Ranibizumab is a 48-kD monoclonal antibody fragment that inhibits VEGF and is specifically formulated for intraocular use. Ranibizumab was first approved by the FDA for the treatment of neovascular AMD in June of 2006. Aflibercept, another variant of anti-VEGF drugs used for intravitreal injection, received FDA approval in November of 2011 for treatment of neovascular AMD, and then garnered subsequent approvals for other indications.

While each of these chemicals works in a different way to inhibit blood vessel growth, bevacizumab continues to be the drug of choice for the majority of US retina specialists and their patients. According to the ASRS 2015 Preferences and Trends survey, 64% use bevacizumab as first line treatment for AMD, and >80% of US members treat choroidal neovascularization from histoplasmosis and other non-AMD causes with bevacizumab. Many ASRS members started using bevacizumab in 2005 when it first became an option for treating AMD, the leading cause of blindness. Even now, with ranibizumab and aflibercept on the market, it remains their first choice because of its lower cost to patients and their extensive experience using it, backed by clinical evidence that supports its efficacy, stability, and safety.

Efficacy and Safety

While bevacizumab does not have FDA approval for the treatment of eye diseases, its efficacy and safety have been well established by federally-funded head-to-head comparative clinical trials. The first of these National Eye Institute funded trials – Comparison of AMD Treatments Trial (CATT) – found bevacizumab to be non-inferior to ranibizumab in the treatment of AMD with a comparable overall safety profile.^{iii,iv} More recently, the first year results of DRCR.net Protocol T trial found that all 3 anti-VEGF agents, on average, produced substantial visual acuity improvement by 1 month that was sustained through 1 year. In eyes with mild initial vision loss (20/32-20/40, 50% of study eyes), little difference was found in mean visual acuity at 1 year.^v

Moreover, several comparative, retrospective studies have supported the relative efficacy of bevacizumab and have found the real-world infection rate of bevacizumab to be comparable to that of ranibizumab. The latter is particularly noteworthy as these studies were conducted prior to the FDA's increased oversight of compounders.^{vi,vii} Finally, a publication (in press) that documents the University of Miami's Bascom Palmer Eye Institute's experience with bevacizumab reports an infection rate of 0.01% for bevacizumab, compared to 0.02% and 0.03% for ranibizumab and aflibercept, respectively.

A potential reason that bevacizumab may have a lower infection rate is because it is repackaged into syringes within a compounding sterile isolator, rather than being drawn into a syringe at the patient's side, where the environment is less controlled, as is done with ranibizumab and aflibercept. An unintended

consequence of an overly restrictive BUD for bevacizumab may be to discourage repackaging in a sterile environment.

Stability of Bevacizumab

The medical literature is replete with articles that document the use of various methods to assess the potency, purity, and quality of repackaged bevacizumab and confirm that bevacizumab maintains both function and stability for 3 to 6 months.

The results of the first study to test the stability and anti-VEGF activity of bevacizumab, previously withdrawn from a vial and either refrigerated or frozen up to 6 months, were published in 2006. The study compared the percentage of degradation of drug in previously pierced vials stored at 4°C with that of the drug in unpierced vials as well as in plastic syringes at 3 months and 6 months. It also tested the degradation at 6 months of bevacizumab frozen in a vial at -10°C. The study found minimal to no degradation at 1 month, and at 3 months onward, an 8-16% degradation. Degradation of the frozen vial at 6 months was 12 percent. Given the potential error in accurately dosing 0.05 mL of a drug in a clinic setting, a 10% change in drug concentration at 3 months is insignificant.^{viii}

Since 2006, several additional studies have been published that indicate the maintenance of bevacizumab's structural stability, chemical stability, concentration, pharmacological activity, and sterility when stored in syringes under refrigeration and protected from light. For example, the Paul et al study demonstrated that bevacizumab can be safely repackaged in polypropylene syringes and stored up to 3 months at 4°C without alteration of its primary, secondary and tertiary structure.^{ix} Chen et al concluded that if aseptic precautions are followed while using bevacizumab, the remaining contents of multiple-dose vials stored after being pierced at 4 degrees C will remain sterile and stable for up to 6 months. The study further found no molecular weight changes among any of the samples and less than 10 percent degradation at all time periods.^x The Ornek et al study concluded that "storage and multiple use of bevacizumab from single-use vials does not seem to result in microbial contamination."^{xi} Finally, a recent article by Khalili et al reported no significant difference over a 6-month period in the quality of bevacizumab repackaged into prefilled polycarbonate and polypropylene syringes when compared with bevacizumab supplied directly from the vial.

Product Degradation Related to Adverse Events

In the background section of the draft guidance, the agency states "[r]epackaging practices that conflict with approved product labeling have led to product degradation resulting in adverse events associated with impurities in the product." It has been hypothesized that silicone oil is one possible impurity and a possible source of sterile endophthalmitis. However, no study has found a causal relationship between these droplets and endophthalmitis or other adverse events. A study conducted by Bakri and Ekdawi found no adverse side effects associated with the presence of silicone oil droplets and found silicone oil droplets in an eye of a patient who had only received ranibizumab, indicating the droplets emerged from the syringe.^{xii} Moreover, a study by Paul et al found that contamination of the syringe content by silicone oil microdroplets is immediate and does not change significantly over time. These results indicate that BUDs do not need to be limited to prevent further silicone oil contamination.^{xiii}

Importance of Access to Safely Repackaged Bevacizumab

Treatment Options: Access to bevacizumab is important for retina specialists because the three anti-VEGF agents are not interchangeable. As previously mentioned, the anti-VEGF agents work differently and some patients respond better to one treatment than another. Recent clinical data have focused on the potential benefits of each of these 3 agents when care is directed by a retinal specialist and targeted to

each patient's specific anatomic and visual response. This ability to individualize treatment and select the most efficacious agent for each patient has been paramount to our achieving the major improvements we have gained in recovering and maintaining visual acuity and retinal function in our patients with blinding diseases of the retina.

Emergency Supply: Having a small supply of intravitreal bevacizumab for the emergent treatment of conditions such as neovascular glaucoma is the standard of care for retina specialists. Prohibiting emergency supplies by instituting excessively short BUDs that are not based on science would compromise patient safety and could result in patient blindness caused by delays in care.

Cost Considerations: If the FDA does not extend the proposed BUDs, retina specialists will be forced to substitute with aflibercept or ranibizumab and thereby cause the total cost of caring for patients to increase by 300%. The Medicare beneficiary co-pay for Avastin is approximately \$11 whereas the co-pay for an FDA-approved drug is approximately \$400. For patients on a monthly treatment protocol, the cost differential on an annual basis is nearly \$4700. Many patients can't afford to switch to the FDA-approved drugs and would be forced to forgo treatment at the expense of their sight.

From a societal perspective, the loss of access to bevacizumab would be extremely expensive. In its 2011 report, the Office of Inspector General (OIG) determined that "if Medicare reimbursement for all beneficiaries treated (during 2008 and 2009) with Avastin or Lucentis for wet AMD had been paid at the Avastin rate, Medicare Part B would have saved approximately \$1.1 billion, and beneficiaries would have saved approximately \$275 million in copayments." The OIG further advised the Centers for Medicare & Medicaid Services (CMS) to "evaluat[e] coverage and reimbursement policies related to Avastin and Lucentis, as well as broader strategies to control Part B drug expenditures." Since that re-evaluation has not occurred, the FDA-approved alternatives continue to cost approximately \$2000 per dose compared to \$50 per dose of Avastin. Similarly, a recent Health Affairs article predicted a cost savings of \$29 billion over 10 years if bevacizumab is used instead of the FDA-approved alternatives to treat eye diseases.

Other Concerns

The guidance short circuits sterility testing requirements set forth in USP Chapter 71 which state that the results of sterility testing are not "final" until a full 14 days. While the USP Microbiology Expert Committee has analyzed rapid sterility testing methods, it has not endorsed any other testing method other than the 14-day test. Moreover, the FDA has not approved the rapid sterility testing options. From our perspective, shortening the BUD such that sterility testing is impossible is a step in the wrong direction.

RECOMMENDATION

The ASRS recommends that the FDA provide outsourcing facilities the option to extend the BUD of the finished biologic based on the results of the stability testing program. The FDA used this approach when it established the shelf life for the bevacizumab used in the CATT Trial. For that trial, the FDA used stability testing to establish an initial 6-month shelf life that was gradually extended to 2 years.

This approach is also consistent with the draft *Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, which provides for the establishment of a stability program to determine appropriate storage conditions and expiration dates, and requires outsourcing facilities to conduct stability testing to ensure that compounded products remain stable and

sterile through the expiry period. In addition, extending the BUD of a biologic is consistent with the 2008 United States Pharmacopeial Convention statement that “beyond-use dating periods established from product-specific data acquired from the appropriate instrumental analysis are clearly more reliable than those predicted theoretically.”^{xiv}

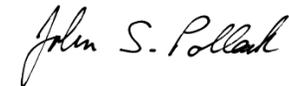
As the outsourcing facilities will be required to meet stringent safety and quality standards that are comparable to drug manufacturing facilities, and will be subject to FDA inspections, we see no compelling reason to prohibit outsourcing facilities from using stability testing to set BUDs for biologics. This approach relies on a process that is already established by the FDA for all other human drugs, and will not result in a significant increase in the Agency’s enforcement costs. Moreover, we believe it is more scientifically based and thus will work equally well for all biologics and mitigate the problem of trying to find a default number for the whole class of biologics.

In summary, if the FDA does not revise the BUDs proposed in the draft guidance, bevacizumab will no longer be available for the treatment of patients with blinding eye diseases. For a chronic disease such as AMD, it is in the patient’s best interest for their doctor to have access to all three anti-VEGF options because some patients respond better to one compared to another. It would be a tragedy for patients to be denied access to an efficacious and safe therapy that has provided cost-effective treatment and saved the sight of millions of patients since 2005. We urge the FDA to provide outsourcing facilities the option to extend the BUD of the finished biologic based on the results of the stability testing program. This approach will likely enable outsourcing facilities to obtain a BUD of at least 3 months for bevacizumab while ensuring the safety, stability and potency of the drug over the expiry period. Please contact Jill Blim, ASRS Executive Vice President, at jill.blim@asrs.org, if you have any questions.

Sincerely,



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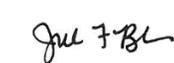
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- ⁱ Draft Guidance on Mixing, Diluting or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application , line 120
- ⁱⁱ Draft Guidance on Mixing, Diluting or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application, footnote 15
- ⁱⁱⁱ The CATT Research Group. Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. *N Engl J Med* 2011; 364:1897-1908.
- ^{iv} Martin DF, Maguire MG, Fine SL, et al; Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmol* 2012;119(7):1388-1398.
- ^v The Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med* 2015; 372:1193-1203.
- ^{vi} Fong DS, Custis, P, Howes, J, Hsu, JW. Intravitreal Bevacizumab and Ranibizumab for Age-Related Macular Degeneration. *Ophthalmol* 2010;117(2):298-302.
- ^{vii} Pilli S, Kotsolis A, Spaide RF, Slakter J, Freund KB, Soreson J, Klancnik J, Coe M. Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an office setting. *Am J Ophthalmol*. 2008;145(5):879-82.
- ^{viii} Bakri SJ, Snyder MR, Pulido JS, McCannel CA, Weiss W, Singh RJ. Six-month stability of bevacizumab (Avastin) binding to vascular endothelial growth factor withdrawal into a syringe and refrigeration or freezing. *Retina*. 2006;(2):519-22.
- ^{ix} Paul M, Viellard V, Roumi E, Cauvin A, Despiau MC, Laurent M, Astier, A. Long-term stability of bevacizumab repackaged in 1 mL polypropylene syringes for intravitreal administration. *Ann Pharm Fr*. 2012;70(3):139-54.
- ^x Chen Y, Wu P, Shiea J, Lo L, Wu Y, Kuo H. Evaluation of the sterility, stability, and efficacy of bevacizumab stored in multiple-dose vials for 6 months. *J Ocul Pharmacol Ther*. 2009;25(1):65-69.
- ^{xi} Ornek K1, Karahan ZC, Ergin A, Tekeli A, Tekeli O. Bevacizumab sterility in multiple doses from a single-use vial. *Ann Pharmacother*. 2008 Oct;42(10):1425-8.
- ^{xii} Bakri SJ, Ekdawi NS. Intravitreal silicon oil droplets after intravitreal drug injections. *Retina*. 2008;28:996-1001.
- ^{xiii} Paul et al. 51.
- ^{xiv} The United States Pharmacopeial Convention. (797) Pharmaceutical Compounding—Sterile Preparations Revision Bulletin. 2008, 40.