Verifying the Source of Compounded Bevacizumab for Intravitreal Injections
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Introduction
The introduction of the vascular endothelial growth factors (VEGF) inhibitors marked a significant breakthrough in the ability to treat ocular diseases, starting with pegaptanib sodium (Macugen®, Valeant Pharmaceuticals North America LLC, Bridgewater, NJ) in December 2004, ranibizumab (Lucentis®, Genentech/Roche, Inc., South San Francisco, CA) in June 2006, and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) in November 2011. All three drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of neovascular age-related macular degeneration (AMD). These anti-VEGF agents have demonstrated improved visual outcomes compared with other therapies and have become the first-line of therapy for treating neovascular AMD.1

Bevacizumab (Avastin®, Genentech/Roche, Inc., South San Francisco, CA) is FDA approved for treatment of some forms of metastatic cancer, and was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection. Because reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off label to treat neovascular AMD and other conditions. The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial to compare the relative safety and effectiveness of ranibizumab (Lucentis) and bevacizumab (Avastin). The study investigated whether a reduced dosing schedule (as needed or PRN) was as effective as a fixed schedule of monthly injections. At one year, the CATT study found that ranibizumab (Lucentis) and bevacizumab (Avastin) had equivalent visual acuity improvements for monthly and as needed dosing.2 Further follow-up at 2 years showed that the two drugs remained comparable in both efficacy and safety, but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year one compared with the two monthly arms, especially in the bevacizumab (Avastin) PRN group.3 Similar results were seen in the 2-year Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial conducted in the United Kingdom.4,5 Presently, there does not appear to be a significant difference in efficacy between ranibizumab (Lucentis) and bevacizumab (Avastin). The systemic safety data in the CATT and IVAN studies are inconclusive.

Background
Bevacizumab (Avastin) is commercially available in a much larger quantity vial than is needed for a single administration for patients with eye disease because it is originally formulated for use in cancer patients. Usually pharmacies then prepare it for multiple dose administration in syringes for subsequent use by ophthalmic practices. This preparation requires aseptic technique and facilities to maintain the sterility of the medication vial and syringes. Compounding pharmacies should comply with the United States Pharmacopeia
(USP) practices, in particular, USP General Chapter <797>: Pharmaceutical Compounding – Sterile Preparations, which is enforceable by the FDA and may also be enforced under §§501 and 502 of the Federal Food, Drug and Cosmetics Act (FDCA).

The intent of the USP <797> guidelines is to reduce the risk of infection caused by pharmaceutical products. The Pharmacy Compounding Accreditation Board (PCAB) accredits pharmacies that provide evidence of adherence to quality standards for pharmacy compounding. The PCAB requires proper licensure with state and federal regulatory authorities, appropriate training of personnel, and facilities and methods that provide aseptic compounding of sterile preparations, which meet the USP <797> guidelines.

Description of the Problem
In the summer of 2011, four separate clusters of infectious Streptococcus endophthalmitis associated with the injection of bevacizumab (Avastin) were identified in Los Angeles, Miami, Minneapolis, and Nashville.6,7 One cluster was limited to a Veteran Affairs (VA) hospital, two were in the community and one was in a VA hospital and in the community. In response, the FDA warned health care professionals that the repackaging of sterile drugs without proper aseptic technique could compromise product sterility, and that they should ensure that drug products are obtained from appropriate, reliable sources and properly administered.8 The FDA also encouraged health care professionals to report any adverse events, side effects, or product quality problems related to the use of repackaged bevacizumab (Avastin) to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program.

Sourcing Recommendations
To reduce the risk of infection to patients, the following steps are recommended when sourcing bevacizumab (Avastin) for intravitreal injections:

- Select a compounding pharmacy accredited by the PCAB, which adheres to quality standards for aseptic compounding of sterile medications (USP <797>). Please note: PCAB does not track or keep record of specific medications that a pharmacy can compound.
- Record the lot numbers of the medication in the patient’s record and in a logbook or spreadsheet in case the numbers are needed for tracking later.

In addition, Ophthalmic Mutual Insurance Company’s (OMIC) Risk Management Recommendations for Preparations of Avastin specify:

- Using proper aseptic technique during the preparation and administration of the injection.
- “Credentialing” the compounding pharmacy where you send the prescription for intravitreal bevacizumab (Avastin) by:
  - Verifying that the compounding pharmacy is licensed/registered in the state it is dispensing.
Inquiring how the pharmacy compounds bevacizumab (Avastin). (The pharmacy should state that it complies with USP <797>.)

- Asking the pharmacy if it is an accredited compounding pharmacy.
- Requesting that the compounding pharmacy prepare the medication for ophthalmic use, confirms the dose and sterility, identifies a syringe suitable for the protein, provides storage and “beyond-use” instructions, and indicates the vial lot number.

**Patient Care Recommendations**

The informed consent process should include a discussion of the risks and benefits of treatment and treatment alternatives where the off-label status of bevacizumab (Avastin) for neovascular AMD should be included in the discussion. (For more information, see [OMIC’s Informed Consent for Avastin (Bevacizumab) Intravitreal Injection](#).)

Treated patients should be instructed to report symptoms of endophthalmitis, retinal detachment, or decreased vision, and should be re-examined promptly.

For more information on patient safety, see:


**References**


4. Chakravarthy U, Harding SP, Rogers CA, et al. IVAN Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular

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