The Latest on Repackaging of Biological Products:

Repackaging of Avastin® for the Treatment of Retinal Diseases

Industry Bulletin
September 2018

Introduction

In January of 2018, the FDA issued its final guidance on the repackaging of biological products. This guidance, in development for over one year, has required FDA-registered outsourcing facilities to develop new methods for repackaging Avastin, a vital medication for the treatment of retinal diseases. This bulletin describes the background behind the FDA's action and chronicles one 503B outsourcing facility's journey to meet the new guidance.

The Birth of 503B Outsourcing Facilities

An outbreak of fungal meningitis at the New England Compounding Center in September 2012 focused the attention of the FDA and Congress on how drugs are compounded in the United States – specifically, how we can be assured that compounded drugs are safe, effective and commercially available, and how we can more easily track drugs through the supply chain.

An important consequence of the outbreak was the Drug Quality and Security Act (DQSA), signed into law in November 2013. The DQSA created two distinct types of compounding categories in sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act. Section 503A applies to licensed physicians and pharmacists who compound for individual patients based on a prescription. The 503A category did not fundamentally change compounding standards or requirements for traditional compounders. However, section 503B established a new category, outsourcing facilities, that could compound and repackage medications in the absence of a prescription as long as they complied with the more stringent requirements of current good manufacturing practice, or cGMP.

The FDA's intent in authorizing outsourcing facilities was to more effectively meet provider needs for safe and compliant office stock of non-patient-specific drugs.[1] Within this context, the repackaging of Avastin has faced challenges due to the biological nature of its active molecule and the route of administration. As a result, meeting the requirements of the 2018 final repackaging biologics guidance ("Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application")[2] has proven to be a costly and challenging endeavor for 503B outsourcers.

1 https://www.fda.gov/NewsEvents/Speeches/ucm577484.htm
2 FDA Guidance for Industry "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application," January 2018

Intraocular Use of Avastin (Bevacizumab)

Avastin, a monoclonal antibody VEGF inhibitor discovered by Genentech, was developed for solid tumor indications. In 2006, when Genentech launched Lucentis® (ranibizumab), the first VEGF inhibitor intended for use in wet age-related macular degeneration (AMD), ophthalmologists had already discovered that Avastin worked just as well, albeit off-label.[3] Moreover, its cost per dose was a fraction of the cost of Lucentis.[4] This led large purchasers like the U.S. Department of Veterans Affairs and smaller purchasers like community eye clinics and two- or three-person ophthalmologist practices to begin treating their macular degeneration patients with Avastin.

According to a 2017 survey by the American Society of Retina Specialists' Global Trends in Retina, Avastin is globally the most commonly used first-line drug for most retinal diseases.[5]

Yet, despite its widespread acceptance and use, few practitioners are aware of, or require Avastin repackagers to comply with, the FDA's 2018 final repackaging biologics guidance. This inattentiveness to compliance could have continued detrimental effects on patient safety.

- In the United States alone, Avastin is used 68 percent of the time in a new wet AMD patient.
- 69 percent of ophthalmologists use Avastin as initial therapy in patients with central retinal vein occlusion (CRVO) with macular edema, VA = 20/70.
- Over 70 percent of physicians would use Avastin as first-line treatment in a 72-year-old patient with branch retinal vein occlusion (BRVO) with macular edema, VA = 20/60.

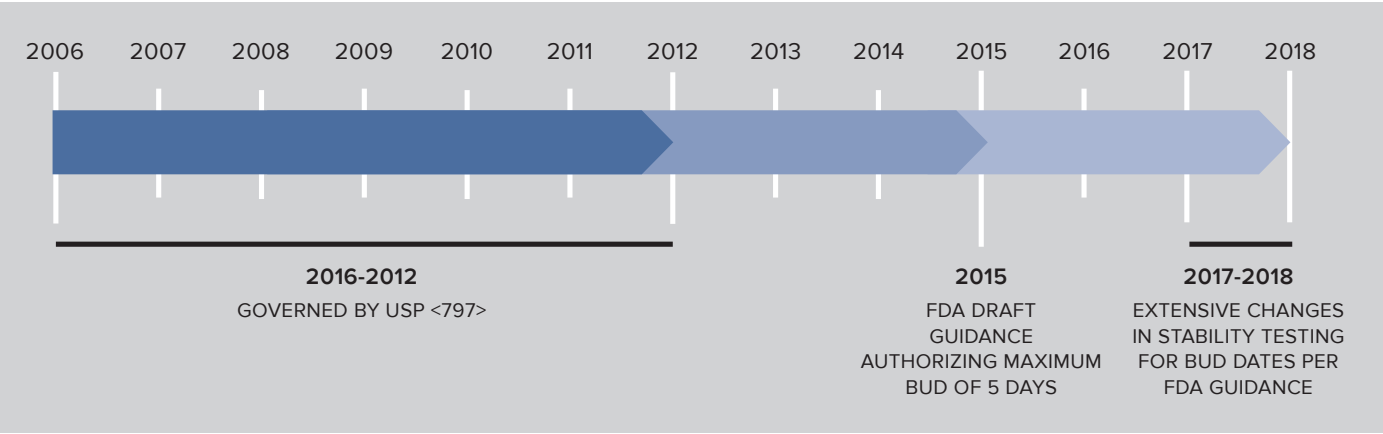
Regulatory History of Repackaging of Avastin

Prior to the DQSA, most pharmacists considered the repackaging of injectable drugs to be a pharmacy compounding function governed by the United States Pharmacopeia (USP) General Chapter <797>.

In 2015, the FDA recognized the need to provide some industry guidance to compounders and issued draft guidance on enforcement discretion for repackaging biologics such as Avastin, authorizing a maximum five-day dating (BUD) with closure integrity testing.

Subsequently, and likely resulting from the continued large number of infectious endophthalmitis cases, along with recognition that Avastin was approved for solid tumors and not as an ophthalmic solution, the FDA modified its earlier guidance and in 2017 issued more extensive draft guidance for repackaging of biological products outside the scope of an approved biologics application.[6]

Timeline of FDA's Guidance on Repackaging Biologics



3 Avastin Doesn't Blind People, People Blind People, Gonzalez, Serafin et al, American Journal of Ophthalmology, Vol 153, Isue 2, 196 – 203e1.
4 Gonzalez, et. al.
5 https://www.asrs.org/content/documents/2017-asrs-global-trends-in-retina-survey-results.pdf
6 https://www.fda.gov/downloads/drugs/guidances/ucm434176.pdf

The 2017 draft guidance became final in January 2018, mandating the following stability indicating tests to establish the BUD of repackaged biological products:

- Subvisible particles
- Protein content
- Product-related impurities including protein aggregation, size and charge variants
- Potency using validated methods
- Sterility tests at additional time points
- pH

In addition, the following tests must be performed for batch release testing:

- Sterility
- Endotoxin
- Color
- Clarity
- Visible particulates
- Subvisible particulates

A 503B outsourcing facility repackaging Avastin must also meet cGMP requirements to ensure that the biological product remains stable and maintains appropriate package integrity during shipping.

Practical Effects of 2018 Final Repackaging Biologics Guidance

Avastin was neither developed nor manufactured to be an ophthalmic. It was developed for solid tumor indications and is being used off label in wet AMD. Not surprisingly, according to Hoffmann-La Roche, bevacizumab is manufactured to meet the requirements for particulate matter in injections, USP <788>,[7] not the more stringent requirements for particulate matter in ophthalmic solutions under USP <789>. As a result, in repackaged Avastin, silicon oil microdroplets and protein aggregates have been a recurring issue.[8]

Acceptance Criteria USP <788> vs. Acceptance Criteria USP <789>

LIGHT OBSCURATION

TEST METHOD USP <788>	DIAMETER		
	≥ 10µm	≥ 25µm	≥ 50µm
# PARTICLES	6000/CONTAINER	600/CONTAINER	N/A

TEST METHOD USP <789>	DIAMETER		
	≥ 10µm	≥ 25µm	≥ 50µm
# PARTICLES	50/mL	5/mL	2/mL

MICROSCOPIC

TEST METHOD USP <788>	DIAMETER		
	≥ 10µm	≥ 25µm	≥ 50µm
# PARTICLES	3000/CONTAINER	300/CONTAINER	N/A

TEST METHOD USP <789>	DIAMETER		
	≥ 10µm	≥ 25µm	≥ 50µm
# PARTICLES	50/mL	5/mL	2/mL

Figure 1

The FDA's 2018 final repackaging biologics guidance addresses some of these concerns. To be compliant, repackaging of Avastin must comply with USP <789>. The Pharmacopoeial standards for the manufacture of intravitreal injections (e.g., Lucentis) are different from those for intravenous administration (e.g., Avastin) with respect to the amounts of subvisible particles permitted. The USP manufacturing requirements for intravenous drug formulations (USP <788>) permit higher subvisible particulate counts than those for ophthalmic solutions (<USP 789>), by a significant magnitude. *See Figure 1.*

Due to the route of administration differences between an injection and an ophthalmic solution, the FDA's 2018 final repackaging biologics guidance requires repackagers of Avastin to meet the more stringent particle requirements of ophthalmology solutions (USP <789>) and other standards for repackaging biologics.[9]

Yet, the possibility remains that many repackagers may still not be compliant with the higher standards.

7 Hoffmann-La Roche Ltd., F. (2016). Application for the deletion of bevacizumab (Avastin®) on the WHO Model List of Essential Medicines. 21st Expert Committee on the Selection and Use of Essential Medicines, 1-6.

8 Effects of Long term Storage and Product Mishandling, Univ. of Colorado; Feb 2011

9 FDA Guidance for Industry "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application," January 2018.

Leiters Meets Regulatory Change Head On

Leiters, founded in 1926, has a long history of evolving and innovating to meet the latest regulatory requirements and market needs. Since the 1980s, Leiters has focused on ophthalmic drugs, such as eye drops, and topical formulations, and later added injectables, including repackaged Avastin.

Consistent with its long-standing commitment to innovation in compounding ophthalmology products, in 2017 the company responded to the FDA's draft guidance for the repackaging of biological products by launching an extensive development process to meet the higher quality and safety requirements governing the repackaging of Avastin.

To comply with the new particle requirements for repackaging a biological ophthalmology product, Leiters uses an optimized aseptic process and a carefully selected syringe. While removing silicone is essential for compliance, more than the use of a silicone-free syringe is required to meet the 2018 final repackaging biologics guidance.

Leiters prides itself on its compliance with regulatory change. For instance, in addition to adhering to the 2018 final repackaging guidance, Leiters' processes under Section 503B are designed to ensure the highest quality outsourced products, consisting of the following elements:[10]

- Prior to commercialization, each new product completes a development process including independent laboratory confirmation of identity, potency and sterility
- Use of aseptic processes and sterile filtration during production to enhance Sterility Assurance Level (SAL)
- Beyond Use Dates (BUDs) established based on product-specific stability testing of both chemical and microbiological characteristics
- Potency, bioburden, endotoxin and sterility testing by an independent laboratory on 100 percent of lots produced
- Independent laboratory testing of chemical and microbiological characteristics including ID, bioburden and endotoxin of all incoming active and inactive ingredients

In an era of rapid regulatory change and heightened demand for high quality compounded and repackaged drugs, Leiters, an FDA-registered 503B outsourcing facility, has emerged as a leader. Specializing in ophthalmology and hospital-based services, Leiters provides repackaged Avastin in compliance with the FDA's 2018 final guidance for the repackaging of biologics.

Industry Call to Action

From both a regulatory and a commercial standpoint, Leiters stands ready to serve the wider ophthalmologic community with sterile preparations of the highest quality. However, it will require diligence to ensure the highest quality of repackaged Avastin, a critical product for intravitreal injection that is used to combat age-related macular degeneration. It is incumbent upon all constituents to ensure the highest quality of the repackaged product.

- All repackagers of Avastin must comply with the 2018 final repackaging biologics guidance and elevated standards for repackaging.
- The FDA must enforce compliance with its issued 2018 final repackaging biologics guidance.
- Physicians and other purchasers of repackaged Avastin must insist upon and purchase repackaged Avastin from repackagers that can affirmatively demonstrate, with published data, compliance with the 2018 final repackaging biologics guidance, most notably USP <789>.

It is imperative that all three groups do their part to ensure the ophthalmologic community and patients are receiving compliant repackaged Avastin.

10 https://leiters.com/503-outsourcing