DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable H. Morgan Griffith
U.S. House of Representatives
Washington, D.C. 2015-4609

JUL 2 8 2015

Dear Mr. Griffith:

Thank you for your letter of June 12, 2015, cosigned by several of your colleagues, concerning FDA's draft guidance document, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (BLA)*. You expressed concerns that "certain provisions, specifically, the beyond-use dates (BUD) for products covered in this guidance, could severely impact physicians' and patients' ability to access these [compounded and repackaged] products." You also state that "[u]nnecessarily restrictive BUDs, particularly when there is strong evidence showing the biological products can be safely mixed, diluted, or repackaged for use with longer BUDs, will essentially eliminate these products as treatment options for many patients."

FDA appreciates the concerns you have raised regarding access to mixed, diluted, and repackaged products addressed in our draft guidance, and specifically the BUDs that FDA proposed. Biological products may provide a rich media for microbial growth, and as noted in the draft guidance, generally, biological products have a complex set of structural features essential to their intended effect and are very sensitive to changes to their manufacturing process, including, but not limited to, any manipulation outside their approved container-closure systems. Many biological products are particularly sensitive to storage and handling conditions and can break down or aggregate if exposed to heat and/or light, if dropped, or if shaken during storage and handling. Accordingly, diluting or mixing a biological product with other components, or repackaging a biological product by removing it from its approved container-closure system and transferring it to another container-closure system is, in the absence of manufacturing controls, highly likely to affect the safety and/or effectiveness of the biological product. Some of these effects, such as microbial contamination and interactions with the container-closure systems, can worsen over time.

The BUDs in the draft guidance reflect FDA's scientific judgment, after consultations with stakeholders, of an appropriate time within which it is reasonably likely that a mixed, diluted, or repackaged biological product could be safely used without significant risks to patients. FDA has included the BUDs in draft guidance in order to provide an opportunity for public comment.

Some of the biological products subject to the guidance, such as bevacizumab, which you reference, are sterile drugs that are manufactured without a preservative. Therefore, it is important that they be handled under conditions designed to maintain their sterility, and if they are repackaged, it is particularly important that they be placed into a suitable container and used quickly to avoid degradation of the product or proliferation of contamination, if the product is inadvertently contaminated during repackaging. Since 2007, FDA has received reports of over 100 patients with wet macular degeneration, who experienced adverse events, including

blindness and serious eye infections, after injections of bevacizumab that may have been contaminated while being repackaged.

As you may be aware, the comment period on the draft guidance closed on May 20, 2015. FDA received over 350 comments, many concerning the BUDs. In addition, in April 2015, FDA held its second series of listening sessions with over 50 stakeholder groups to hear their views about FDA's efforts to implement the Drug Quality and Security Act and related activities, such as repackaging biological products. FDA intends to consider all comments on the draft guidance and input received during the recent stakeholder listening sessions before finalizing the draft guidance.

Thank you, again, for contacting us concerning this matter. Please let us know if you have further questions. The same letter has been sent to your cosigners.

Sincerely,

Thomas A. Kraus
Associate Commissioner for Legislation