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May 20, 2015

Stephen Ostroff, M.D.  
Acting Commissioner of Food and Drugs  
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: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application; Draft Guidance for Industry.***

Dear Dr. Ostroff:

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, and our 43,000 individual members, the American Hospital Association (AHA) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance "Mixing, Diluting, or Repackaging Biological Products<sup>1</sup> outside the Scope of an Approved Biologics License Application." We also applaud the FDA for holding listening sessions to ensure that stakeholders, including hospitals and health care systems, have the opportunity to provide in-person input into the draft guidance.

**The AHA is concerned that the proposed "beyond-use-dates" (BUDs) are inappropriately short and may limit patient access to critical biological products. The AHA urges the FDA to address this concern, thereby helping to ensure that high-quality and safely mixed, diluted and repackaged biological products continue to be provided to patients without disruption.**

The preparation of mixed, diluted or repackaged biological products, both sterile and non-sterile, is a fundamental part of pharmacy practice in hospitals and health care systems. As the FDA recognizes in the draft guidance, certain licensed biological products may need to be mixed or diluted in a way that is not described in their approved labeling in order to meet the needs of a specific patient. For example, for some biological products there is no licensed pediatric strength

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<sup>1</sup> A "biological product" is defined in the Public Health Services Act as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."



or dosage form so the product must be diluted for use in pediatric patients. In addition, licensed biologic products are sometimes repackaged, by removing them from their original container and placing them in a different container(s), such as for pediatric or ophthalmic use.

Hospitals and health care systems often purchase mixed, diluted or repackaged biological products from other organizations, including outsourcing facilities. However, in order to ensure patient safety and the timely availability of appropriate medications for procedures and patient care, it also is critical that hospitals are able to continue to mix, dilute or repackage biological products in-house or centrally within health care systems. For instance, such in-house preparations are needed if there is no manufactured unit-dose or commercial product of the type needed by patients, or if the biological product is needed immediately. Having these biological products available in a properly labeled unit-of-use form in hospitals and health care systems increases patient safety, reduces waste, improves the hospital's control of biological distribution, and increases ease of use and efficiency of care.

In the draft guidance, the FDA describes the conditions and requirements that would have to be met in order for state-licensed pharmacies (e.g., hospital or health care system pharmacies) and outsourcing facilities to be able to prepare biological products without violating the Public Health Services Act or the Food, Drugs and Cosmetics Act. One of these conditions imposes limits on BUDs – the date after which the biological product is not to be used. **The AHA is concerned that the proposed BUDs are inappropriately short.**

Specifically, for biological products that are mixed, diluted or repackaged in state-licensed pharmacies or in outsourcing facilities, the proposed BUD is up to 24 hours if successful microbial challenge studies are performed in the type of container in which the biological products will be packaged, or no more than four hours if such studies are not performed. In addition, the proposed BUD is up to five days for biological products repackaged by outsourcing facilities if the facilities conduct adequate compatibility studies on the container-closure system (e.g., the syringe) to ensure product integrity.

These extremely short BUDs would result in increased waste of biological products, potentially creating shortages and limiting access to biologics for patients, including access to important biological products such as repackaged bevacizumab (Avastin, a critical drug used in the clinical management of wet age-related macular degeneration); mixed doses of infliximab (Remicade, used to treat autoimmune diseases such as rheumatoid arthritis); mixed doses of rituximab (Rituxan, used to treat leukemia and lymphoma); and many other lifesaving products. Currently, hospitals and health care systems utilize longer BUDs that are based on the U.S. Pharmacopeia Convention Chapter 797 as well as available evidence, including peer-reviewed literature. These sources show that these biological products remain stable, sterile and effective with BUDs longer than those proposed by the FDA when following standardized aseptic process to ensure sterility, stability and safety.

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**The AHA recommends the FDA change the draft guidance to permit longer BUDs if successful stability and sterility testing are conducted or if the validated evidence is available from well-designed, published, independent studies that show increased sterility and stability in the same type of environment.**

Thank you again for the opportunity to comment. If you have any questions, please contact me or Roslyne Schulman, director for policy development, at (202) 626-2273 or [rschulman@aha.org](mailto:rschulman@aha.org).

Sincerely,

/s/

Linda E. Fishman

Senior Vice President

Public Policy Analysis and Development