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May 20, 2015

Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO 51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

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Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics Licensing Application; Draft Guidance for Industry (Docket No. FDA-2014-D-1525)

Dear Drs. Ostroff and Woodcock:

Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters nationwide, submits these comments on the draft guidance document titled "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics Licensing Application" (the draft guidance).[1]

We support the issuance of a guidance covering repackaging of biological products. Improperly repackaged biological products, particularly sterile biological products, present a serious public health risk, and it is imperative that the Food and Drug Administration (FDA) establish clear

[1] Food and Drug Administration. Mixing, diluting, or repackaging biological products outside the scope of an approved biologics licensing application. Guidance for industry (draft Guidance). February 2015.

guidance for industry in this area. Repackaging of biological products raises particular concerns due to the widespread repackaging of bevacizumab (Avastin), a biological product approved for cancer treatment but commonly repackaged for intraocular injection to treat wet age-related macular degeneration (wet AMD), an unapproved, or "off-label," use. Between 2010 and 2013 there have been at least three large-scale outbreaks of infection linked to contaminated bevacizumab.[2,3,4] The largest of these outbreaks led to loss of vision in 11 patients.[5] In addition, a compounding error in a hospital pharmacy in 2011 led to brain damage and/or vision loss for five patients after bortexamib (Velcade) was accidentally packaged and labeled as bevacizumab for intraocular injection.[6] Bortexamib is a biologic used in cancer treatment and not intended for intraocular injection. There have likely been additional patient injuries not reported in the medical literature.

Repackaged bevacizumab and other repackaged, mixed, or diluted biological products pose considerable risk to patients. Public Citizen advises consumers to avoid use of products prepared by compounding pharmacies and outsourcing facilities, including repackaged bevacizumab, wherever possible, due to risk of contamination and potential errors. Instead, we advise consumers to use only FDA-approved drugs and licensed biological products, except in cases where a person has an individualized need requiring medication to be specially tailored for his or her use (such as an allergy to one of the ingredients in an FDA-approved or -licensed product). There are currently two biological products licensed by the FDA for treatment of wet AMD: ranibizumab (LUCENTIS) and aflibercept (EYLEA), and we urge patients with this condition to use one of these two drugs.

Nevertheless, demand for repackaged bevacizumab remains enormous, in part because this drug is far less costly than FDA-approved alternatives, which are not available in generic form and remain excessively expensive. Public Citizen estimates that over 6 million doses of bevacizumab

[2] Frost BA, Kainer MA, Eye opening: Are compounding pharmacies causing harm? Presented at the Society for Healthcare Epidemiology of America 2011 Annual Scientific Meeting, Dallas, April 1-4, 2011. http://www.ismp.org/docs/paper4263.pdf. Accessed May 14, 2015. "Pharmacy A" was located in Tennessee as it was inspected by officials from the Tennessee Department of Health, and patient injuries occurred in 2009 and 2010, and were also likely in Tennessee as the pharmacy was described as "local" to the eye clinic where the injections were administered. *Ibid. See also* Frost BA, Kainer MA. Safe preparation and administration of intravitreal bevacizumab injections. *N Engl J Med.* 2011;365:2238.

[3] Food and Drug Administration. Warning Letter to Clinical Specialties Compounding Pharmacy. June 27, 2014. http://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm416208.htm. Accessed May 14, 2015. Clinical Specialties was located in Georgia, and patient injuries occurred in Indiana and Georgia, likely in spring 2013. *Ibid.*

[4] Goldberg RA, Flynn HW, Miller D, etc. Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: One-year outcomes and investigative results. *Opthalmology.* 2013;120(7):1448-53.

[5] *Ibid*.

[6] Department of Veterans Affairs Office of Inspector General. Healthcare inspection, oversight review of ophthalmology adverse drug events, VA Greater Los Angeles Healthcare System, Los Angeles, California. April 12, 2012. Report No. 12-01515-151.

are repackaged for intraocular injection annually in the United States.[7] It is therefore essential for the FDA to take steps to ensure the quality and sterility of repackaged biological bevacizumab and other biological products. Given this background, we support the FDA's proposal, outlined in the draft guidance, to require that the mixing, diluting or repackaging of biological products be carried out in accordance with United States Pharmacopeia (USP) Chapter <797> (for pharmacies or federal facilities) or requirements for current good manufacturing practices (CGMP) (for outsourcing facilities).[8]

We also support the requirement that biological products repackaged in pharmacies or federal facilities, but not outsourcing facilities, be held for distribution pending receipt of a prescription for an identified individual patient, as opposed to releasing large batches of the products to be held in health care facilities (a practice commonly referred to as creating "office stock"). While individualized repackaging by compounding pharmacies serves an important health care function, large-scale drug repackaging for office stock is a manufacturing activity that should only be carried out under CGMP. The best way to ensure compliance with CGMP is to require submission of a biological product licensing application (BLA) for FDA approval. Current law also now permits companies registered as outsourcing facilities to repackage drugs without submitting BLAs, but they must do so in compliance with CGMP. Companies seeking to engage in large-scale repackaging for office stock should therefore either develop and submit a BLA or register as an outsourcing facility.

We support the implementation of federal "beyond use date" (BUD) requirements for sterile diluted, mixed, or repackaged biological products. However, we are concerned that some of the BUD periods described in the draft guidance may be too long. The FDA has recommended a standard BUD of four hours for biological products mixed, diluted, or repackaged in a compounding pharmacy or mixed or diluted in an outsourcing facility, with the possibility to extend that time up to 24 hours if microbial challenge studies performed on the formulation of diluted, mixed, or repackaged biological product demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD.[9] We agree with the FDA that the four-hour time period is likely appropriate, given that four hours is consistent with the labeling of many licensed biological products, which generally require disposal of any products not used within four hours after the product has been reconstituted or the container has been entered.[10] While we have some concerns with extending this window to 24 hours, risk to patients will be adequately mitigated if companies comply with the requirement of performing adequate microbial challenge studies.

The draft guidance allows for much longer BUD periods for biological products repackaged at outsourcing facilities: up to five days for repackaged biological products, provided the facility

[7] Bevacizumab has been estimated to account for roughly 60 percent of the market for wet AMD, a disease that affects over 1.6 million people in the United States. Patients require, on average, seven injections of bevacizumab per year in order to maintain vision.

[8] Food and Drug Administration. Mixing, diluting, or repackaging biological products outside the scope of an approved biologics licensing application. Guidance for industry (Draft Guidance). February 2015.

[9] *Ibid*.

[10] *Ibid*.

conducts "adequate compatibility studies on the container-closure system."[11] The guidance justifies these longer periods as follows:

> This longer BUD reflects that outsourcing facilities must comply with CGMP requirements and are subject to FDA inspections on a risk-based schedule. Conditions maintained to comply with CGMP requirements provide greater assurance of the quality of manufacturing operations and the products that are produced at the facility.[12]

While we agree that CGMP requirements, if implemented, would provide greater assurance of quality, including the sterility of drugs, we question whether outsourcing facilities are, in fact, currently compliant with CGMP. FDA inspectors observed "significant objectionable conditions," including CGMP violations.[13] At least three outsourcers have received more than one 483 following multiple inspections, and 15 have received warning letters alleging violations of federal law, including violations of CGMP. It is evident from these ongoing compliance issues that quality and sterility is not assured at a majority of outsourcing facilities. Given this background, the BUD period for these facilities should be shortened to align with current BUDs for compounded drugs, with the potential to amend the guidance in the future should the FDA find that all, or nearly all, registered outsourcing facilities are found consistently to be in compliance with CGMP.

In addition, we are concerned that the guidance is ambiguous regarding the starting point of the BUD period, which should begin at the moment the container closure of the original licensed biological product is breached, a step that could potentially introduce contamination to the sterile product. The current guidance does not specify the start date of the various BUD periods.[14] We note that the repackaging process involves multiple steps, beginning when the original container closure is breached and ending when the final repackaged product is sealed by means of a new container closure system. Certain pharmacies may extend this multistep process over days or even weeks, in particular when repackaging bevacizumab.[15] Such time delays should be minimized to reduce the risk of contamination and biological growth. Yet because such delays have been known to occur, it would be helpful for FDA to clarify that the starting point for the BUD period begins at the moment the container closure of the original licensed biological product is breached.

Thank you for the opportunity to comment on this important public health matter.

Sincerely,

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[11] *Ibid*.
[12] *Ibid*.
[13] Food and Drug Administration. Registered outsourcing facilities. Updated as of May 1, 2015. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm. Accessed May 15, 2015.
[14] Food and Drug Administration. Mixing, diluting, or repackaging biological products outside the scope of an approved biologics licensing application. Guidance for industry (Draft Guidance). February 2015.
[15] Food and Drug Administration. Warning letter to Infupharma, July 30, 2012. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm317190.htm. Accessed May 14, 2015.

Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Michael Carome, M.D.
Director
Public Citizen's Health Research Group