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May 20, 2015

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Department of Health and Human Services
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Janet Woodcock, M.D.
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Center for Drug Evaluation and Research
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities; Draft Guidance for Industry (Docket No. FDA-2014-D-1524)

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consumer advocacy organization with more than 350,000 members and supporters nationwide, submits these comments on the draft guidance document titled "Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities" (the draft guidance).[1]

We support the issuance of a guidance covering repackaging of drug products. Improperly repackaged drugs, particularly sterile drugs, present a serious nationwide public health risk, and

[1] Food and Drug Administration. Repackaging of certain human drug products by pharmacies and outsourcing facilities (draft guidance). February 2015.

it is imperative that the Food and Drug Administration (FDA) establish clear federal guidance for industry in this area.

In general, we support the draft guidance, particularly the efforts by the FDA to ensure the sterility of repackaged drugs by requiring that repackaging be carried out in accordance with either the United States Pharmacopeia (USP) Chapter <797> (for pharmacies and federal facilities) or requirements for current good manufacturing practices (CGMP) (for outsourcing facilities).[2]

We also support the requirement that drugs 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 drugs 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 new drug application (NDA) for FDA approval. Current law also permits companies registered as outsourcing facilities to repackage drugs without submitting NDAs, which allows them to legally manufacture drugs provided the facilities meet certain requirements, including compliance with CGMP. Companies seeking to engage in large-scale repackaging for office stock should therefore either develop and submit an NDA or register as an outsourcing facility.

We support the implementation of federal "beyond use date" (BUD) requirements for sterile repackaged drugs. However, we are concerned that some of the BUD periods described in the draft guidance for FDA-approved sterile drug products without an in-use time or for unapproved sterile drug products are too long. The USP recommends that sterile drugs compounded under "medium risk" conditions be given a BUD of 30 hours if stored at controlled room temperature, nine days if stored in a refrigerator, or 45 days if stored in a solid frozen state between –25°C and –10°C.[3] The FDA has determined that sterile repackaging presents risks comparable to medium-risk sterile compounding, and therefore proposes that these same time periods be applied to drugs repackaged in compounding pharmacies. These BUD periods are likely appropriate. However, the guidance also allows for much longer BUD periods for drugs repackaged at outsourcing facilities: up to 28 days for repackaged drugs stored either at room temperature or in a refrigerator, and up to 59 days if stored in a solid frozen state. The guidance justifies these longer periods as follows:

> These longer BUDs reflect 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.[4]

[2] *Ibid*.
[3] *Ibid*.
[4] *Ibid*.

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 actually compliant with CGMP at the present time. We note that among 44 currently registered outsourcing facilities that have been inspected by the FDA, all but one received a form FDA-483 at the close of its inspection, indicating that FDA inspectors observed "significant objectionable conditions," including CGMP violations.[5] 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 for FDA-approved sterile drug products without an in-use time or unapproved sterile drug products, which should begin at the moment the container closure of the original FDA-approved drug is breached, a step that could potentially introduce contamination to the sterile product. The current guidance does not make this clear: Regarding drugs repackaged in pharmacies, the guidance does not specify the start date of the BUD period.[6] Regarding drugs repackaged at outsourcing facilities, the guidance specifies that the start date of the BUD period will occur either at the "time of repackaging" or at the "completion of the sterility test."

We note that the repackaging process typically 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. We know based on past FDA inspection reports that some pharmacies may extend this multistep process over days or even weeks.[7] 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 FDA-approved drug is breached.

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[5] 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.

[6] Food and Drug Administration. Repackaging of certain human drug products by pharmacies and outsourcing facilities (Draft guidance). February 2015.

[7] 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. While this warning letter specifically addressed repackaging a biological product, similar factors are involved in the repackaging of sterile drugs.

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

Sincerely,

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