THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

March 13, 2017
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Draft Guidance: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2017 Revision; Docket No. FDA-2014-D-1525-0357)

Dear Sir or Madam,

The Pew Charitable Trusts is pleased to offer comments on the Food and Drug Administration's (FDA) revised draft guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including that of compounded drugs.

We support the FDA's proposal to allow certain manipulations of commercial biological products. The guidance appropriately recognizes that there may be circumstances when a biologic must be diluted, mixed or repackaged outside of the labeling instructions in order to meet a clinical need, such as adjusting the concentration or packaging of the medicine for pediatric or ophthalmic use. However, the guidance also appropriately reinforces that beyond-use dates (BUDs), when specified by the labeling instructions, must be followed and cannot be extended by additional sterility testing. If the product label does not establish dating for repackaged product, the BUD cannot exceed 24 hours. The new draft guidance improves upon FDA's earlier proposal by providing compounders that comply with Good Manufacturing Practices (GMP) the ability to set BUDs for repackaged biological products that are longer than the 24 hour limit in FDA's guidance where such extended dating is supported by testing; this proposal strikes a reasonable balance between the practical advantages of longer dating and the need to ensure product sterility.[1]

Extended beyond-use dates for repackaged biological products should be supported by testing

Biological products merit consideration different from chemical compounds. Because biologics are produced from living organisms, they are particularly susceptible to microbial growth. Furthermore, they cannot be terminally sterilized through typical methods because the active biological substance can

[1] Pew's comments of FDA's earlier February 2015 proposal are available in the docket: https://www.regulations.gov/document?D=FDA-2014-D-1525-0261. These comments address only the testing/dating provisions that are new to this proposal.

be damaged through those processes. Biological products can also be damaged if improperly handled or stored. Any mixing, diluting or repackaging of a biologic outside of approved labeling instructions, storage times, or conditions can create uncertainty about product integrity. Using a diluent other than those specified in labeling, for example, can change microbial growth potential.

Biological products can be also costly and may not be ordered in predictable volumes. Therefore, extended beyond-use dating can serve a practical need for preparing and repackaging these products.

Given the sensitive nature of biological products, and the pragmatic need for extended dating that does not compromise patient safety, we support FDA's proposal to permit longer dating for repackaged biological products under conditions that support product integrity and sterility.

As repackaging, mixing or diluting a biologic outside the scope of label instructions could raise product integrity and sterility issues over time, the process for establishing beyond-use dating – the time by which a preparation must be used before it is at risk for degradation, inactivation, contamination or interaction with its container – must include careful testing. Adequate studies are necessary to permit any longer-term dating in order to properly assess the impact of this extended use time. Microbial challenge studies, for example, are critical to sterility testing of these products and addressed in this draft guidance. These studies are designed to measure the time before which a contaminated drug product will show microbial growth that could subsequently harm a patient.

The guidance document's defined set of conditions for stability and release testing (Appendices A and B) give outsourcing facilities guidance for setting BUDs for repackaged products based on controlled testing. Repackaged products tested within these criteria can have BUDs longer than the 24 hour default in FDA's guidance. We support FDA's inclusion of both visual inspection tests for color, clarity and presence of particulate matter, which are visible markers of product quality, and chemical tests for product integrity and sterility. Accordingly, we support allowing outsourcing facilities that comply with Good Manufacturing Practices (GMP) to assign dating for specific repackaged (not mixed or diluted products, for which dating instructions are typically in the product labeling) biological products if meaningful studies demonstrate product stability for that time period and integrity of the new container-closure system, and if there is confidence that sterility has been maintained during the repackaging process.

Ability to set BUDs for repackaged products through testing should be tied to higher quality standards

The risk of product integrity issues will necessarily vary depending on how a product is made. Outsourcing facilities are subject to stringent quality standards — GMP standards – that are analogous to the standards that apply to pharmaceutical manufacturers. As a result, **FDA's proposal to permit greater flexibility for only those compounders that adhere to higher quality standards is reasonable.**

The GMP standards help ensure that compounded products are consistently stable and sterile, which is important for the preparation of biological products due to their sensitive nature. Key requirements for outsourcing facilities include:

- Stability Studies: The draft guidance on GMP for outsourcing facilities released in 2014 sets an expectation for a stability program, parameters for stability studies and an expectation that the results of stability testing be used to determine appropriate storage conditions and expiration dates. Biological products can degrade or lose potency over time or through improper handling or storage, making a stability program important to confirm the integrity of these products.
- Sterility Testing: To be GMP-compliant, outsourcing facilities must also be able to demonstrate to the FDA that they have robust and validated aseptic production processes, to ensure sterility in the final product. Once robust processes provide confidence in finished product sterility, beyond-use dating can appropriately be set by assessing product stability and container integrity, as FDA has proposed.
- Mechanisms to Track Harm: In addition to GMP compliance, outsourcing facilities registered with the FDA must also follow reporting and labeling requirements, including adverse event reporting, which would help enable FDA to spot trends if extended dating led to patient harm.

Beyond-use dating must follow approved labeling when specified

Approved labeling has undergone systematic review and FDA approval and contains instructions that have resulted from specific testing by the manufacturer. Thus, the draft guidance appropriately requires that, for state-licensed pharmacies or Federal facilities, if a product label specifies the time in which a product must be used after it is opened or mixed, the BUD cannot exceed that "in-use" time specified in the label, or the expiration date of the product. Outsourcing facilities may establish BUDs that extend beyond the "in-use" time *if* that BUD is supported by testing, but, even they cannot exceed the expiration date provided by the manufacturer, which is important to ensure that the product remains potent and stable. **The extension of beyond-use dating based on testing performed by outsourcing facilities provides practical benefits, but should not supersede the expiration date of the product.**

* * *

The revisions to this draft guidance on mixing, diluting or repackaging biologic products balance practical benefits with safety measures based on appropriate testing criteria. Thank you for your efforts to protect patients through robust implementation of the Drug Quality and Security Act, and for your consideration of these comments.

Sincerely,

Kathy Pham, Pharm.D.
Senior Officer, Drug Safety Project

Elizabeth Jungman, J.D., M.P.H.
Director, Public Health Programs