



May 20, 2015

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 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**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's Draft Guidance for Industry "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

**I. General Comments:**

BIO applauds the issuance by the Food and Drug Administration (FDA) of the Draft Guidance entitled, "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application." (Draft Guidance)<sup>1</sup> The policies and recommendations set forth in the Draft Guidance, when finalized, represent critical steps forward in the effort to protect patients from biological products prepared under conditions that could result in their contamination or a lack of effectiveness.

As BIO has noted in previous comments to FDA regarding compounding<sup>2</sup>, we strongly believe that the drug compounding provisions of the Drug Quality and Security Act (DQSA) did not alter current law with regard to biologics and that therefore there is still no applicable exemption in the Food, Drug, and Cosmetic Act (FD&C Act) compounding provisions for entities that compound or repackage biological products. As such, BIO is pleased that FDA reiterated in its Draft Guidance that "[a] biological product that is mixed, diluted, or repackaged outside the scope of an approved BLA is an *unlicensed biological product* under

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<sup>1</sup> 80 Fed. Reg. 8881 (Feb. 19, 2015).

<sup>2</sup> "BIO Comments on FDA Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act" February 3, 2014 located [here](#), and "BIO Comments on FDA Draft Guidance for Industry on Current Good Manufacturing Practices—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and Cosmetic Act" September 2, 2014 located [here](#).



section 351 of the [Public Health Service] PHS Act.”<sup>3</sup> This means that such a product lacks the assurances of safety, purity, and potency provided by FDA licensure, which requires extensive studies and considerable analytical, preclinical, and clinical data as well as detailed information about the methods, equipment, and controls used to manufacture the product and ensure its quality. Moreover, once a biological product is removed from its approved container-closure system in the absence of appropriate manufacturing controls, it is “highly likely to affect the safety and/or effectiveness of the biological product.”<sup>4</sup>

For this reason, the manipulation of licensed biological products should be limited to instances where medically necessary to meet the specific needs of individual patients and such manipulation is performed under conditions that will help to ensure the quality of the resulting product. We are also concerned with FDA’s stated policy of enforcement discretion, which we elaborate in detail in the section below.

In particular, we wish to highlight our strong support for the Draft Guidance’s establishment of standards for beyond-use dating (BUD).<sup>5</sup> BIO agrees that such standards are critical to ensuring product quality for biological products, which the Agency recognizes as “particularly susceptible to microbial proliferation over time, if contaminated.”<sup>6</sup> Specifically, we find the BUD standards established for biological products mixed or diluted by outsourcing facilities (*i.e.*, up to 24 hours with appropriate microbial challenge studies) are appropriate in light of the high risks to patient safety posed by such products. However, while we support the BUD in the Draft Guidance in general, BIO is concerned by the proposed 5 day BUD for a product that is repackaged by an outsourcing facility when “adequate compatibility studies on the container-closure system” is done. The justification for such a BUD is unclear. We acknowledge that the BUD standard of up to 5 days could be scientifically appropriate if the Draft Guidance clarifies that certain conditions must be met:

- Repackaged drug product solutions are prepared as sterile solutions;
- The requirement for appropriate microbial challenge studies, as further risk mitigation in the rare event that sterility is not maintained, (to support a 24-hour BUD), along with the compatibility studies on the container-closure<sup>7</sup> (to support a 5-day BUD), are both fulfilled;
- The repackaged biological product is stored and shipped according to the licensed product labeled storage conditions, including refrigeration where directed (*e.g.*, 2-8° C);

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<sup>3</sup> Draft Guidance at Lines 177-78 (emphasis is the original).

<sup>4</sup> *Id.* at Lines 100-102. We note that the Draft Guidance does not explicitly consider that changes in a biological product’s primary container can affect container closure integrity and drug stability (*i.e.*, proteins can adsorb to glass, excess silicone or other coating can desorb from the container wall and may even cause immunogenicity issues, etc.), and we urge FDA to further evaluate these safety concerns in finalizing the Draft Guidance.

<sup>5</sup> See *id.* at Lines 320-359.

<sup>6</sup> *Id.* at Lines 322-323.

<sup>7</sup> Purity and quality product characteristics should be assessed by more than one method, including physicochemical stability, container closure integrity, material compatibility for leachables/extractables and sterility of the stored drug. See International Conference on Harmonisation (ICH), Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Q5C (Nov. 30, 1995) (“On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity and potency of the product will be detected.”).



- The overall quality assessment of the impact of the repackaging on the overall quality of the drug product is addressed; and
- Outsourcing facilities comply with any and all good manufacturing practice (cGMP) requirements, sterility regulations, and state laws.

These and other controls are essential because many biological products provide optimum conditions for microbial growth and can result in dangerous levels of contamination in the product within a short period of time.

## **II. Comments on Specific Provisions of the Draft Guidance:**

Although FDA's Draft Guidance represents a strong first step in putting measures in place to help ensure the safety and quality of biological products that are mixed, diluted, or repackaged in a manner that is not consistent with their approved BLAs, there are several issues raised in the Draft Guidance that BIO believes would benefit from additional clarification or refinement. We present those issues below along with suggested resolutions for FDA's consideration.

### **A. Exercise of Enforcement Discretion for Outsourcing Facilities That Mix, Dilute, or Repackage Biological Products**

The Draft Guidance states that "FDA does not intend to take action for violations of sections 351 of the PHS Act or 502(f)(1) of the [Federal Food, Drug, and Cosmetic] Act if a state-licensed pharmacy, a Federal facility, or an outsourcing facility mixes, dilutes, or repackages a biological product in accordance with the conditions described [in the Draft Guidance], and any applicable requirements."<sup>8</sup>

BIO is concerned by this articulation of FDA's enforcement policy, which greatly expands the scope of an outsourcing facility's activities envisioned under the Compounding Quality Act.<sup>9,10</sup> That law, section 503B of the FD&C Act, exempts an outsourcing facility from the misbranding and unapproved new drug provisions of the law only with respect to drugs approved under section 505 of the FD&C Act. Biological products were not included among the products that could be compounded by outsourcing facilities, as FDA acknowledges in the Draft Guidance: "biological products licensed under section 351 of the PHS Act are not eligible for the statutory exemptions offered by sections 503A or 503B of the FD&C Act, and if a facility registers as an outsourcing facility but only mixes, dilutes, or repackages such biological products, none of the products made at the facility will be eligible for the exemptions under section 503B."<sup>11</sup>

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<sup>8</sup> Draft Guidance at Lines 280-283; *see also id.* at n.11.

<sup>9</sup> Title I of the Drug Quality and Security Act, Pub. L. No. 113-54 (2013).

<sup>10</sup> The expansion appears to vitiate the commercial value for manufacturers that produce and get approval for new containers or devices for administration of biologics, or for any distribution or licensing arrangements for new packaging with other manufacturers. In both these cases, the new delivery systems must meet higher standards met by manufacturers. *See also United States of America versus Baxter Healthcare Corporation and Glaxo Specialties.*

<sup>11</sup> Draft Guidance at n.11.



Thus, in enacting the Compounding Quality Act, Congress determined that the requirements imposed on outsourcing facilities in section 503B (e.g., registration, drug reporting, labeling, and facility inspection) were sufficient to permit the safe compounding of traditional drugs, but Congress made no such determination with respect to biological products, which were conspicuously excluded from section 503B. With the Draft Guidance, however, FDA announces that it will extend enforcement discretion to outsourcing facilities that elect to also mix, dilute, and repackage biological products. In so doing, FDA does not require outsourcing facilities to perform these activities only after receiving a valid prescription, a condition that the Draft Guidance imposes on state-licensed pharmacies and Federal facilities that mix, dilute, and repackage biological products.<sup>12</sup> BIO urges FDA to reconsider and amend this position, which greatly expands the scope of an outsourcing facility's permissible activities beyond what Congress envisioned when it enacted the Compounding Quality Act. We also believe it would be helpful for FDA to discuss their planned enforcement strategy for when they do take action against a compounding entity.

Additionally, we would like FDA to confirm that the list of conditions in the Draft Guidance is an "and list" not an "or list." In other words, any compounding entity that is mixing, diluting, or repackaging biologics must meet *all* of the listed conditions, as well as all other applicable requirements, not only some of the listed conditions. If an entity only meets some of the listed conditions, we would assume that FDA would take appropriate enforcement action.

## **B. Mixing, Diluting, or Repackaging a Single Dose Vial Into Multiple Units**

The Draft Guidance states that a biological product packaged in a single dose vial can be mixed, diluted, or repackaged into multiple units, as long as it is not mixed, diluted, or repackaged in a way that otherwise conflicts with the approved labeling, except for the statements designating the product as a single dose or single use product.<sup>13</sup> As noted above, BIO does not believe that the drug compounding provisions of DQSA altered current law with regard to biologics and that therefore there is still no applicable exemption in the FD&C Act compounding provisions for entities that compound or repackage biological products; this would include repackaging single dose vials into multiple units. Single dose vials that have been repackaged into multiple units have not been tested for safety and efficacy at these new dosage levels and for new indications and as such this activity is inappropriate and should not be allowed under the Draft Guidance.

Additionally, BIO is concerned about the inconsistency between this new position regarding repackaging and longstanding FDA views on the appropriate procedures and considerations with regard to biologics sterility<sup>14</sup> as well as control of components and drug product containers and closures, including those for specific classes of drugs as applicable.<sup>15</sup> BIO recommends that if FDA is going to allow for this repackaging activity they indicate in the Final Guidance that repackaged biological products should satisfy the same sterility

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<sup>12</sup> See *id.* at Lines 298-306.

<sup>13</sup> *Id.* at Lines 315-318.

<sup>14</sup> 21 CFR §610.12

<sup>15</sup> 21 CFR §211 Subpart E and 21 CFR §200 Subpart C



requirements and all regulations related to control of components and drug product containers and closures in place for products manufactured under an approved BLA (e.g. 21 CFR §610.12, 21 CFR §211 Subpart E and 21 CFR §200 Subpart C).

### **C. Adverse Event Reports and Complaints**

In line with BIO's position that biological products should not be included in a guidance describing the mixing, diluting, or repackaging outside of a BLA, BIO is also concerned with the link between the original manufacturer and the repackager, and how this link is viewed by FDA. BIO interprets such activities as decoupling the two since the mixed, diluted, or repackaged product is no longer representative of the original product and constitutes a different product subject to its own adverse event reporting. Thus, the linkage for Adverse Event Reporting, and likewise complaint handling, between the original manufacturer and the repackager is not assured and the original manufacturer should not be responsible for reporting or investigating adverse events associated with the use of their products that have been mixed, diluted or repackaged outside of their BLA. BIO requests FDA to carefully consider the implications and requirements for adverse event reporting in light of these consequences.

BIO supports the Draft Guidance's recommendation that each outsourcing facility report serious adverse events to FDA that may be associated with its mixed, diluted, or repackaged biological products.<sup>16</sup> Although we note that FDA has issued a separate Draft Guidance addressing adverse event reporting for outsourcing facilities that compound drugs under section 503B,<sup>17</sup> we ask that FDA make explicit in this Draft Guidance that it is holding outsourcing facilities that mix, dilute, or repackage biological products to the same adverse event reporting standards to which FDA holds the manufacturers of other drugs marketed without approved new drug applications. These important requirements are set forth in 21 CFR § 310.305 and mirror those in 21 CFR § 600.80 applicable to manufacturers of licensed biological products. They include the obligations to "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA," maintain adverse drug experience records for a ten-year period, and permit FDA to inspect and copy those records.<sup>18</sup> In addition to adverse event reporting, BIO recommends that outsourcing facilities be held to the same standards for product complaint handling pursuant to 21 CFR §211.198 and product recalls pursuant to 21 CFR §7 Subpart C to which FDA holds the manufacturers of drugs marketed with approved applications.

BIO believes that the necessary clarification for both adverse event reporting and complaints could be accomplished by revising text in the Draft Guidance to read:

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<sup>16</sup> Draft Guidance at Lines 431-432.

<sup>17</sup> FDA, Draft Guidance for Industry – Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Feb. 2015).

<sup>18</sup> 21 CFR § 310.305(a), (f)(1)-(3). It is clear that these requirements are applicable because the Draft Guidance directs at Lines 378-80 that the "name of the outsourcing facility" be on the labeling for the product, and the requirements in 21 CFR § 310.305(c)(1) apply to "[a]ny person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor."



“The outsourcing facility promptly reports to FDA (including any follow-up reports) and investigates serious adverse events ~~to FDA~~ that may be associated with its mixed, diluted, or repackaged biological products in accordance with 21 CFR § 310.305 and Agency guidance. In addition, the outsourcing facility complies with the requirements for product complaint handling related to its mixed, diluted, or repackaged biological product in accordance with 21 CFR § 211.198, as well as associated biological deviation reporting to FDA (per 21 CFR §600.14) and/or product recalls (per 21 CFR §7 Subpart C).”<sup>19</sup>

This proposed language outlines the full scope of an outsourcing facility’s adverse event reporting and complaint obligations and provides clear direction for identifying the relevant criteria for such reports, which in turn will facilitate each outsourcing facility’s satisfaction of this important postmarketing obligation.

#### **D. Shipping Validation**

The Draft Guidance notes that “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.”<sup>20</sup> It further explains that “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.”<sup>21</sup>

BIO agrees with FDA’s assessment of these risks associated with the mixing, diluting, and repackaging of biological products. Quality concerns also extend, however, to the transportation of these products, which the Draft Guidance does not address. BIO recommends that FDA require outsourcing facilities to follow shipping validation processes—an obligation that manufacturers of biological products must satisfy—to ensure that product quality is not compromised during shipment. Holding outsourcing facilities to this same rigorous standard is in the interest of public health, as the use of unvalidated shipping and transport containers can introduce contaminants or lead to stability issues that present significant health risks to patients.

#### **E. Microbial Challenge Studies**

BIO notes that there seems to be an underlying assumption that diluted and compounded drug product solutions will have some degree of microbial contamination (*i.e.*, sterility is NOT maintained), rather than focusing on proper aseptic handling to ensure that sterility is maintained. The Draft Guidance discusses microbial challenge studies and reference to “unacceptable level” of microbes<sup>22</sup>. This also suggests that there are acceptable levels of

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<sup>19</sup> See Draft Guidance at Lines 431-32.

<sup>20</sup> *Id.* at Lines 96-98.

<sup>21</sup> *Id.* at Lines 99-102.

<sup>22</sup> *Id.* At Lines 320-337.



microbes which implies that a lack of sterility is acceptable. BIO strongly believes that such a suggestion is inappropriate. It is critical that any diluted or compounded drug products must be sterile in order for safety and efficacy to be maintained. This guidance should indicate that diluted and compounded drug product solutions are expected to be prepared as sterile solutions, and that the microbial challenge studies are further risk mitigation in the rare event that sterility is not maintained.

### **III. Conclusion:**

BIO appreciates this opportunity to comment on the Draft Guidance for Industry "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett  
Managing Director, Science and Regulatory Affairs  
Biotechnology Industry Organization (BIO)



**SPECIFIC COMMENTS**

<b><u>SECTION</u></b>	<b><u>ISSUE</u></b>	<b><u>PROPOSED CHANGE</u></b>
<b>I. INTRODUCTION AND SCOPE</b>		
<b>II. BACKGROUND</b>		
A. <i>BIOLOGICAL PRODUCTS</i>		
B. <i>LEGAL FRAMEWORK FOR FDA'S REGULATION OF BIOLOGICAL PRODUCTS</i>		
C. <i>SECTIONS 503A AND 503B OF THE FD&amp;C ACT DO NOT EXEMPT BIOLOGICAL PRODUCTS FROM THE PREMARKET APPROVAL REQUIREMENTS OF THE PHS ACT OR FROM PROVISIONS OF THE FD&amp;C ACT</i>		
D. <i>HOSPITAL AND HEALTH SYSTEM REPACKAGING OF DRUGS IN SHORTAGE FOR USE IN THE HEALTH SYSTEM (SECTION 506F OF THE FD&amp;C ACT)</i>		
<b>III. POLICY</b>		
A. <i>GENERAL CONDITIONS</i>		
B. <i>MIXING, DILUTING, OR REPACKAGING LICENSED BIOLOGICAL PRODUCTS</i>		
<b>Lines 295-296:</b>	The Draft Guidance highlights that one of the conditions for applicability of this Draft Guidance is that the "biological product is mixed, diluted, or repackaged in a state-licensed pharmacy, a Federal facility, or an outsourcing facility."	BIO suggests that language should be included in this section that refers to the need for a controlled environment (e.g., laminar flow) as described in USP <797> to clarify conditions under which these activities occur to ensure patient safety.
<b>Lines 311-318:</b>	The Draft Guidances discusses that a biological product cannot be mixed, diluted, or repackaged in a way that conflicts with the approved labeling for the approved product.	BIO asks FDA to clarify what would be considered conflicting with the approved label. For example would the each of the following be in conflict with the approved label: <ul style="list-style-type: none"> <li>• Changes to product dosing;</li> <li>• Changes in product formulation;</li> <li>• Use for a non-label, unapproved indication; or</li> <li>• Repackaging for an "off-label" use.</li> </ul>
<b>Lines 320-321:</b>	The Draft Guidance states that "biological products are very susceptible to product quality concerns when mixed, diluted, or repackaged."	BIO suggests that reference be made for the need to ensure facilities and controls are in place to ensure product is not contaminated during operations and that the product meets quality standards after operations are completed.



<b><u>SECTION</u></b>	<b><u>ISSUE</u></b>	<b><u>PROPOSED CHANGE</u></b>
<b>Lines 360-364:</b>	The Draft Guidance states that products mixed, diluted, or repackaged in an outsourcing facility, must be done in accordance with current good manufacturing practice (CGMP) requirements.	<p>BIO asks FDA to confirm that outsourcing facilities must establish CGMPs in advance of any mixing, diluting, or repackaging of a biological product.</p> <p>Additionally, we ask FDA to clarify the following points:</p> <ul style="list-style-type: none"> <li>• How will lots be determined?</li> <li>• Is each vial considered a bulk drug substance which must trace its lineage back to original manufacture?</li> <li>• How will sterility be determined?</li> <li>• Will sterility be assessed in the context of the customary CGMP standards?</li> </ul>
<b>Lines 370-372:</b>	The Draft Guidance discusses that such products may be distributed only in states in which the facility mixing, diluting, or repackaging the biological product meets any applicable state requirements.	<p>BIO believes it should be made clear that such products must meet all state requirements, as such we recommend editing the text to read:</p> <p>“9. The mixed, diluted, or repackaged biological product is distributed only in states in which the facility mixing, diluting, or repackaging the biological product meets any <a href="#">and all</a> applicable state requirements.”</p>
<b>Lines 414-416:</b>	The Draft Guidance discusses that the label should include Directions for Safe Use.	BIO asks FDA to clarify that the Directions for Safe Use on mixed, diluted, or repackaged biological products should be limited to the FDA approved label.
<b>Lines 422-429:</b>	The Draft Guidance discusses the required 6-month report for outsourcing facilities.	BIO believes that absolute traceability of each outsourced product is essential to assess safety as well as compliance to BUD requirements.
<b>Lines 431-431:</b>	The Draft Guidance discusses outsourcing facilities reporting of serious adverse events.	BIO recommends that outsourcing facilities be held to the same adverse event reporting standards to which FDA holds the manufacturers of other drugs marketed without approved new drug applications as well as to the same standards for complaint handling. As such, we suggest the following edit to the text (as amended per earlier

<u>SECTION</u>	<u>ISSUE</u>	<u>PROPOSED CHANGE</u>
		<p>comments):</p> <p>"The outsourcing facility <a href="#">promptly reports to FDA (including any follow-up reports) and investigates</a> serious adverse events <del>to FDA</del> that may be associated with its mixed, diluted, or repackaged biological products <a href="#">in accordance with 21 C.F.R § 310.305 and Agency guidance. In addition, the outsourcing facility complies with the requirements for product complaint handling related to its mixed, diluted, or repackaged biological product in accordance with 21 C.F.R § 211.198, as well as associated biological deviation reporting to FDA (per 21 CFR §600.14) and/or product recalls (per 21 CFR §7 Subpart C)."</a></p>
<i>C. LICENSED ALLERGENIC EXTRACTS</i>		
<b>IV. APPENDIX 1—MICROBIAL CHALLENGE STUDY DESIGN</b>		