March 14, 2017

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

Re: Docket No. FDA-2014-D-1525-0357: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application; Revised Draft Guidance For Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's revised draft Guidance for Industry "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application."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BIO supports the FDA's issuance of the Revised Draft Guidance entitled, "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application" (Revised Draft Guidance).[1] We remain firmly committed to the view that measures like those set forth in the Revised Draft Guidance, when finalized, represent critical steps forward in the effort to protect patients when biological products are handled in a manner that is inconsistent with their approved labeling and that could result in contamination or a lack of effectiveness.[2]

BIO agrees that "biological products are particularly sensitive to storage and handling conditions" and that "diluting[,] mixing . . . or repackaging a biological product . . . is, in the absence of manufacturing controls, highly likely to affect the safety and/or effectiveness of the biological product."[3] Thus, BIO is pleased to see that FDA has responsively addressed many of the concerns raised in comments on the previous draft of the guidance. Specifically, BIO agrees that the following are among the minimum necessary conditions for attempting to safeguard the quality of a biologic removed from its approved container-closure system:

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[1] 82 Fed. Reg. 4358 (Jan. 13, 2017).
[2] BIO Comments on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application, Docket No. FDA-2014-D-1525, May 20, 2015 & Mar. 7, 2016.
[3] Revised Draft Guidance at 3 (Lines 100–06).

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- All repackagers must make a formal assessment of the suitability of the container closure used for the repackaged product.[4] This assessment helps ensure that the repackaged container does not compromise the integrity of the biological product after it is repackaged.

- State-licensed pharmacies and Federal facilities must complete repackaging in four hours or less.[5] A four-hour in-process time for repackaging activities helps limit the risk for contaminating or destabilizing the repackaged biological product.

- Outsourcing facilities should establish stability programs and conduct scientifically meaningful release testing.[6] Stability testing is necessary to ascertain whether the mixed, diluted, and repackaged biologic will continue to meet critical quality attributes for the duration of the BUD, and release testing helps reduce the risk of releasing compromised or contaminated biological products that have been manipulated outside of the conditions set forth in their approved labeling.

- Outsourcing facilities must ensure that biological products remain stable and maintain appropriate package integrity during the shipping process.[7] This helps ensure end-to-end stability of the biological product so that it remains safe and effective upon reaching the patient.

There remain, however, several issues with respect to mixed, diluted, and repackaged biologics that BIO believes are not appropriately addressed in the Revised Draft Guidance or that would benefit from additional clarification or refinement. Prime among these is that the Revised Draft Guidance still fails to address the criticality of ensuring the sterility of the biological product's primary container closure and its secondary packaging, which is essential to patient safety.

II. Comments on Specific Provisions of the Revised Draft Guidance:

Although the Revised Draft Guidance represents significant progress toward establishing a strategy to help preserve 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 Revised 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 Mixing, Diluting, or Repackaging Biological Products

BIO would like to reiterate that the exercise of enforcement discretion for biological products that are mixed, diluted, or repackaged is fundamentally inappropriate.[8] As FDA concedes in

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[4] *Id.* at 8 (Lines 299–300).
[5] *Id.* at 8 (Lines 307–10).
[6] *Id.* at 11 (Lines 373–75) & Appendices A–B.
[7] *Id.* at 19 (Lines 682–85).
[8] *See* BIO Comments on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application, Docket No. FDA-2014-D-1525, May 20, 2015, at 3–4.

the Revised Draft Guidance: "[F]or purposes of sections 503A and 503B [of the Federal Food, Drug and Cosmetic (FD&C) Act], a drug does not include any biological product that is subject to licensure under section 351 of the [Public Health Safety (PHS)] Act. Accordingly, such biological products are not eligible for the exemptions for compounded drugs under sections 503A and 503B of the FD&C Act."[9] Congress had the opportunity to permit biological products to be among those that could be mixed, diluted, and repackaged by compounding pharmacies and outsourcing facilities but declined to make this possible.[10] Nevertheless, FDA "has developed this guidance to explain the conditions under which FDA does not intend to take action when certain biological products are mixed, diluted, or repackaged in a manner not described in their approved labeling."[11] BIO requests that FDA reconsider its approach to this issue.[12]

B. Ensuring Product, Container, and Packaging Sterility

BIO agrees that "[i]mproper repackaging of drugs and biological products can cause serious adverse events. . . . For example, failure to properly repackage a sterile drug (such as a biological product) under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. . . . These risks are often even more acute for biological products due to their complex composition and sensitivity to variations in storage and handling conditions."[13] BIO adds that not only must the biological product remain sterile, but for many injectable biological products, the primary container closure (and hence its secondary packaging) must remain sterile to ensure that the injection is carried out under the appropriate controlled aseptic conditions.[14]

Given the critical importance for patients of minimizing the potential for infection during administration of mixed, diluted, and repackaged biological products, BIO strongly encourages FDA to explicitly require state-licensed pharmacies, Federal facilities, and outsourcing facilities to take measures to ensure the sterility of a product's primary container closures and, where appropriate, its secondary packaging. For manufacturers, this means rigorous, validated processes and conditions for the sterilization of not only the primary container closure but also delivery dispensers and secondary packaging. No less should be required of compounding pharmacies and outsourcing facilities that remove biologic products from their approved container-closure systems and sterile packaging.[15]

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[9] Revised Draft Guidance at 6 (Lines 213–16).
[10] *See, e.g.,* 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (statement of Sen. Harkin ("[W]e do not change current law regarding repackaging of biologics. The Senate bill established a new regulatory regime for repackaging and biologics, but ultimately, after our bipartisan, bicameral discussions, we made no changes to current law on those subjects . . . .").
[11] *Id.* (Lines 224–26).
[12] Indeed, as recently as 2013, FDA held a dim view of the manipulation of biological products by compounding facilities. *See Examining Drug Compounding: Hearing Before the H. Subcomm. on Energy & Commerce* 113th Cong. 20-21 (2013) (statement of Dr. Janet Woodcock, Director, CDER) ("FDA believes that with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include . . . most biologics . . . .").
[13] Revised Draft Guidance at 4 (Lines 123–27).
[14] *See, e.g.,* 21 C.F.R. § 200.50(a)(c) ("Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles . . . should be packaged so as to maintain sterility until the package is opened…").
[15] Compounding pharmacies and outsourcing facilities that include multiple units in one package (e.g., a single plastic bag for multiple pre-filled syringes), rather than sterile individual unit packaging would likely not meet this

Additionally, BIO believes that certain product sterility requirements must be strengthened to protect patients. BIO supports FDA's inclusion of Appendices A and B of the Revised Draft Guidance, which require outsourcing facilities wishing to extend the beyond use date (BUD) for repackaged biological products to conduct stability and release testing to ensure compliance with CGMP requirements.[16] BIO specifically supports FDA's decision to require that Appendix A's stability testing include sterility and container closure integrity tests.[17] Nevertheless, as written, these stability and release tests do not hold mixed, diluted, and repackaged injectable biological products to the same standards of external sterility as injectable biological products released by the manufacturer. Once again, this is a matter of serious safety concern for patients.

For example, as written, the container closure integrity test applies only to the primary container, and it is optional if the outsourcing facility chooses to conduct an additional sterility test at "additional time points."[18] As BIO stated above, ensuring container sterility is critical for ensuring patient safety in the case of certain injectable biological products, and ensuring container sterility requires appropriate secondary packaging. Therefore, BIO recommends that FDA amend this section to additionally require that, for injectable biological products required to be administered under aseptic conditions: (1) container sterility testing is conducted at the time of mixing, diluting, and repackaging; and (2) secondary packaging integrity testing is conducted at specified time points to ensure the sterility of the enclosed container. Further, BIO is concerned that under Appendix B, an outsourcing facility must only "*initiate* sterility testing before release."[19] It is dangerous to release a potentially non-sterile biological product (or where applicable, a biological product in a non-sterile container), especially if such product is likely to be used shortly after release, potentially before sterility results are received. Therefore, BIO strongly urges FDA to require that sterility testing be *completed* before release.

C. Enforcement of CGMP Requirements

BIO supports robust safeguards to ensure product stability and sterility, but BIO is concerned that many outsourcing facilities are failing to meet the minimum standards recommended by the Revised Draft Guidance and other current good manufacturing practices (CGMP) standards. BIO requests that FDA explicitly state that it will not exercise enforcement discretion when it recognizes that outsourcing facilities are failing to meet the Revised Draft Guidance and CGMP requirements in their mixing, diluting, and/or repackaging activities.

Further, BIO encourages FDA to prioritize inspections of outsourcing facilities that mix, dilute, and repackage biologics because of the inherent risks associated with such activities. Pre--approval inspections for compliance with CGMP are conducted before a manufacturer of

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standard because of the potential for the units remaining in the multi-unit package to be contaminated when the sterile barrier is broken to remove the first unit for use.

[16] Revised Draft Guidance at 17–21.

[17] *Id.* at 19 (Lines 671–78).

[18] *Id.* (lines 676–78).

[19] *Id.* at 20 (Line 709) (emphasis in original).

a biological product may have its BLA approved and introduce its product to the market.[20] The Revised Draft Guidance, however, is silent on whether outsourcing facilities will be inspected for CGMP compliance if they engage in the sale of products that have been mixed, diluted, or repackaged in a manner not described in their approved labeling. This should be a precondition to FDA's exercise of enforcement discretion for such activities. Finally, given the significant potential for the contamination of biological products, those outsourcing facilities that engage in these operations should be subject to more frequent FDA inspection to ensure continued compliance with CGMP and the recommendations in the Revised Draft Guidance.

D. In-Time Use Limitations

Finally, BIO agrees with FDA's decision to apply in-use time limitations consistent with the approved product's labeling to repackaging activities.[21] The Revised Draft Guidance requires that, "[i]f the biological product is mixed, diluted, or repackaged by a State-licensed pharmacy or a Federal facility, it is given a BUD that does not exceed the time within which the opened product is to be used as specified in the approved labeling of the licensed biological product for *any* manipulation ('in-use time') or the expiration date of the biological product being mixed, diluted, or repackaged, whichever is shorter."[22] In a footnote example, FDA applies a biological product's labeled "in-use time" following dilution as the BUD following repackaging of the biological product. BIO agrees with this approach, which recognizes the risk of product contamination following "*any* manipulation" of the biological product. BIO therefore understands this requirement to mean that, unless a biological product's label specifically states the in-use time for a repackaged biologic, the BUD will be the same as any labeled in-use time for the diluted or mixed product.

III. Conclusion:

BIO appreciates this opportunity to comment on the Revised 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/

Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

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[20] 21 C.F.R. § 601.20(d) ("A biologics license shall be issued or a biologics application approved only after inspection of the establishment(s) listed in the biologics application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations.").
[21] *Id.* at 9 (Lines 321–27) & n.16.
[22] *Id.* at 9 (Lines 321–27) (emphasis added).

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. POLICY		
B. MIXING, DILUTING, OR REPACKAGING LICENSED BIOLOGICAL PRODUCTS		
Lines 286–90; 338–41:	The Revised Draft Guidance allows a single-dose vial to be mixed, diluted, or repackaged inconsistent with its labeling to the extent that the labeling designates the product as a single-dose or single-use product. It also allows an outsourcing facility, after mixing, diluting, or repackaging a biological product, to assign a BUD up to 24 hours if the approved labeling does not specify an in-use time, and the product is refrigerated.	BIO requests FDA provide clarity on the intent of these paragraphs because they could be read as an FDA endorsement of the off-label use where the approved biological product carries a single-use indication or requires the product to be stored in its original carton (*i.e.*, does not specify an in-use time).
Lines 299–300:	The Revised Draft Guidance requires that the container into which the biological product is mixed, diluted, or repackaged is suitable for storage of the biological product through its BUD.	BIO requests FDA explain how suitability of the container will be determined (*i.e.*, through stability studies, container closure integrity testing, leachable/extractable testing, etc.).
Lines 299–300:	The Revised Draft Guidance requires that the container into which the biological product is mixed, diluted, or repackaged is suitable for storage of the biological product through its BUD.	BIO requests that FDA also require that only diluents from an approved list be used. This would help prevent an inappropriate diluent from being used.
Lines 307–10:	The Revised Draft Guidance requires the duration of time for mixing, diluting, or repackaging in a State-licensed pharmacy or Federal Facility is no more than four hours.	BIO suggests FDA specify a firm duration limit for mixing, diluting, or repackaging in an outsourcing facility.
Lines 307–10:	The Revised Draft Guidance requires the duration of time for mixing, diluting, or repackaging in a	BIO requests clarity regarding the start and end time of the four hours. This four-hour time period could be interpreted as pertaining only to the time between

SECTION	ISSUE	PROPOSED CHANGE
	State-licensed pharmacy or Federal Facility is no more than four hours.	puncturing and end of repackaging, but ought to also include administering to a patient.
Lines 307–10; 328–30:	The Revised Draft Guidance requires the duration of time for mixing, diluting, or repackaging in a State-licensed pharmacy or Federal Facility is no more than four hours.	BIO requests that FDA clarify how the four-hour duration of time for mixing, diluting, or repackaging is related to the 24-hour BUD for refrigerated products. The time for mixing, diluting, and repackaging should be included within the 24 BUD, such that if a product is manipulated for the full 4 hours, it can have a BUD assigned of no more than 20 hours.
APPENDIX A – ASSIGNING A BUD FOR REPACKAGED BIOLOGICAL PRODUCTS BASED ON STABILITY TESTING		
Lines 596–97:	The Revised Draft Guidance requires that outsourcing facilities that repackage biological products must have a written stability program that includes "Evaluation of samples of the biological product in the same container closure system as that in which the product is *marketed*." (emphasis added). The footnote to this line states that "the evaluation of samples of the biological product may be in the same container closure system as that in which the product is *distributed*." (emphasis added).	BIO requests clarification on the meaning of "same container closure system." Specifically, what is the difference between the "same container closure system as that in which the product is *marketed*" and the "same container closure system as that in which the product is *distributed*" in this context?
Lines 642–46:	The Revised Draft Guidance requests the following non-destructive tests to be conducted to ensure product stability: appearance; color and clarity; and visible particulates.	BIO recommends that pH testing also be conducted because monoclonal antibodies are sensitive to pH.
Lines 682–85:	The Revised Draft Guidance requires an outsourcing facility to ensure that the biological product remains stable and maintains appropriate package integrity	BIO requests that FDA provide more specific requirements regarding how the outsourcing facility ensures stability of the biological product. For

SECTION	ISSUE	PROPOSED CHANGE
	during shipping. Specifically, "the outsourcing facility ensures that the shipping temperature does not deviate from the recommended storage temperature range set forth in the approved product labeling for the licensed biological product."	diluted and mixed products, the shipping conditions are typically not included in the approved label, and shipping related stress can have significant negative impact on product quality for biological products, especially after the compositions have been altered. BIO further requests that FDA require a shipping study be performed to "ensure that the biological product remains stable," just as it requires testing to establish a BUD for a repackaged biological product. Finally, BIO requests that FDA specify that products that are required to be maintained at 2-8 degrees Celsius should be, as a matter of CGMP, stored at the required temperature in the outsourcing facility and shipped in conditions that maintain the temperature. Further, processes should be implemented to ensure that temperature is maintained during shipment, and that upon receipt by the doctor's office, the product can be confirmed as not having had a temperature excursion.
Lines 682–85:	The Revised Draft Guidance requires the outsourcing facility to ensure that the biological product remains stable and maintains appropriate package integrity during shipping.	Currently, the Revised Draft Guidance does not mention the ability to confirm receipt of a product by the doctor. BIO recommends that FDA add a provision that ensures the ability to confirm receipt of a product by the doctor. This is a matter of patient safety.
APPENDIX B – RELEASE TESTING FOR BIOLOGICAL PRODUCTS MIXED, DILUTED, OR REPACKAGED BY OUTSOURCING FACILITIES		
Lines 703–14:	The Revised Draft Guidance requires the following release tests be performed on each batch of	BIO recommends that FDA require the following release tests also be performed: pH testing;

SECTION	ISSUE	PROPOSED CHANGE
	biological products repackaged by an outsourcing facility: sterility (initiated); endotoxin; color; clarity; visible particulates; and subvisible particulates.	concentration study; chemical stability; and container closure integrity.
Line 709:	The Revised Draft Guidance requires that sterility testing be *initiated* by the outsourcing facility before release.	As described in the body of the comments, BIO reiterates that FDA ought to require that sterility testing be *completed* prior to release of products. The facility should also have completed a risk assessment in order to detail the controls in place to ensure sterility.
Lines 716–26:	The Revised Draft Guidance requires the following release tests be performed on each prescription set that an outsourcing facility has prepared: sterility; color; and visible particulates.	BIO recommends that FDA require the following release tests also be performed: sub-visible particulates; concentration of the product; chemical stability; and container closure integrity.
General:	It would be meaningful if the guidance addressed ways in which manufacturers of a biological product could mitigate potential risks/concerns when their approved products are used outside the scope of their approved labeling.	