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

Reference: FDA Guidance for Industry Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application **Docket ID**: FDA-2014-D-1525

Dear Sir/Madam:

PDA applauds FDA's efforts to further clarify its policy for these operations and appreciates the opportunity to comment on this draft guidance. PDA recommends this guidance include additional references to USP <797> throughout the document as well as include requirements consistent with GMPs to demonstrate the product was diluted as claimed. A dilution performed at an outsourcing facility should have a verification and a quality check not only on the operation but on the calculation for the dilution or addition as a dilution error may not be noticed before administration.

The length of the scope section now leaves confusion at the end as to which types of products are in or out. It appears that the scope is biologicals and allergenic extracts and would be helpful if this was stated succinctly. PDA also recommends that the scope of the guidance be clearly defined so as to exclude mixing, diluting, repackaging done in the hospital pharmacy or bedside. Please see the attached detail comments for additional rationale and recommendations.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in the practice of pharmacy as well as members representing our Biotechnology Advisory Board and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson

Richard Johnson
President

Food and Drug Administration Draft Guidance

Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved BLA

May 15, 2015

General Comments

General Comments	Rationale
PDA recommends that the scope of the guidance be clearly defined so as to exclude mixing, diluting, repackaging done in the hospital pharmacy or bedside.	There are significant advantages to preparing biological products in the pharmacy where controls including USP <797> can be employed. However, the limit of 4 hours is likely to be exceeded in a large hospital when preparations are made in a central pharmacy for a medication cart that will be exchanged at a nurse's cart. The microbial testing specified in appendix A is more appropriate for an outsourcing facility or large scale compounding operation.
Please clarify which product types are in and out of scope by stating that this guidance applies to biologicals and allergenic extracts.	The length of the scope section now leaves confusion at the end as to which types of products are in or out. It appears that the scope is biologicals and allergenic extracts and would be helpful if this was stated succinctly.
PDA recommends this guidance include additional references to USP <797> throughout the document.	These operations are best handled in an aseptic manner, in an aseptic environment such as a properly performing laminar air flow hood or isolator. It is important that any facilities conduct operations in manner to ensure safety of the patient.
PDA recommends that this guidance include requirements to demonstrate the product was diluted as claimed.	GMPs require a verification of operation and a quality control test. A dilution performed at an outsourcing facility should also follow GMPs with a verification and a quality check not only on the operation but on the calculation for the dilution or addition. A dilution error may not be noticed before administration. (See also comments to line 297)

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale
38-40 plus footnote 3	Removing a biological product from the original container at the point of care for immediate administration to a single patient after receipt of a patient-specific prescription or order for that patient (e.g., drawing up a syringe to administer directly to the patient).	Point of care **or pharmacy within the same hospital**	PDA recommends that it is preferable that a pharmacy make up doses from a multi dose vial under controlled conditions rather than this occurring at the immediate point of care.
250/251and 291, 292, 293	This guidance addresses the mixing, diluting, or repacking of a licensed biological product, ~~not a biological product~~	This guidance addresses the mixing, diluting, or repacking of a licensed biological drug product, **which is not**	PDA recommends clarification of wording for clearer understanding.

Line No.	Current Text	Proposed Change	Rationale
	~~licensed for further manufacturing use only, or a bulk substance.~~	**licensed for further manufacturing.**	
295-296	The biological product is mixed, diluted, or repackaged in a state-licensed pharmacy, a Federal facility, or an outsourcing facility.	The biological product is mixed, diluted, or repackaged **in a controlled environment (laminar flow) as described in USP <797> when prepared in** a state-licensed pharmacy, a Federal facility, or an outsourcing facility.	PDA recommends this clarification to conditions under which the activities must be performed to ensure patient safety.
297	2. The biological product is mixed, diluted, or repackaged in a state-licensed pharmacy, a Federal facility, or an outsourcing facility.	**A dilution performed at an outsourcing facility should also follow good GMPs with a verification and a quality check not only on the operation but on the calculation for the dilution or addition.**	Standard GMPs would require a verification of operation and a quality control test. (see also the general comments)
320	As described in section II of this guidance, biological products are very susceptible to product quality concerns when mixed, diluted or repackaged.	Add the following text in this section. **Facilities and controls should be in place to ensure that the product is not contaminated during operations and that the product meets quality standards after operations have been completed.**	PDA recommends this additional text to ensure patient safety and clarify requirements. Equipment should be qualified and testing control should be implemented.
326	6. As described in Section II of this guidance, biological products are very susceptible to product quality concerns when mixed, diluted or repackaged. NEW a,b,c,d added; existing a and b become e and f	**NEWa. The mixed, diluted, or repackaged biological must be visually inspected before administration to patients to ensure the mixed, diluted, or repackaged biological is free from particles. Do not use if particles are observed.** **NEW b. If mixing or diluting a biological product, use only diluents in the approved BLA.** **NEW c. Mixing a biological should only**	PDA recommends new considerations be added to the beginning of this section to discuss appropriate handling of biologicals to protect against physical or chemical degredation. (a) Biologicals are sensitive to handling; particles may form from aggregates caused by shear, cavitation, or incompatibility with diluent or container closure materials. (b) Solution incompatibility may cause degradation of the biological. (c)Vigorous

Line No.	Current Text	Proposed Change	Rationale
		be done by slowly inverting the combined solution a minimum of 10 times unless directed otherwise in an approved BLA. **NEW d. If repackaging a biological into a syringe for administration, the filled syringe must be visually inspected before administration to ensure the contents are free from particulates.**	mixing has been reported to cause aggregation and particulates. (d) Some biologicals are sensitive to silicone oil, which is frequently present in syringes and on syringe plunger stoppers.
321-324	For example, because biological products provide a rich media for microbial growth, they are particularly susceptible to microbial proliferation over time, if contaminated. Therefore, the mixed, diluted, or repackaged biological product is given a BUD that is not longer than the applicable BUD below:	Therefore, the mixed, diluted, or repackaged biological product **should be prepared as sterile, and as further risk mitigation in the rare event that sterility is not maintained, it** is given a BUD that is not longer than the applicable BUD below:	Need to stress that the sterility of the drug product needs to be maintained.
461	The prescription set is prepared in a physician's office, state-licensed pharmacy, a Federal facility, or outsourcing facility.	**When prepared in a state-licensed pharmacy, a Federal facility, or an outsourcing facility. a controlled environment (laminar flow) as described in USP <797> should be used.**	New text is recommended to describe conditions used to ensure patient safety.
456-481	The conditions referred to in the preceding paragraph are as follows: 1. 2. 3. 4. 5. NEW Number 6 Proposed	**NEW6.a. The mixed, diluted, or repackaged allergenic extract must be visually inspected, where possible, before administration to patients to ensure the mixed, diluted, or repackaged allergenic extract is free from particles. Do not use if particles are observed.** **NEW 6.b. If mixing or diluting an**	PDA recommends new considerations be added to this section to discuss appropriate handling of allergenic extracts to protect against physical or chemical degradation. Similar comments were made above for biological products. (a) Allergenic extracts are sensitive to handling; particles may form from aggregates caused by shear, cavitation, or

Line No.	Current Text	Proposed Change	Rationale
		allergenic extract, use only diluents in the approved BLA. **NEW 6.c. Mixing an allergenic extract should only be done by slowly inverting the combined solution.** **NEW 6.d. If repackaging an allergenic extract into a syringe for administration, the filled syringe must be visually inspected before administration to ensure the contents are free from particulates.**	incompatibility with diluent or container closure materials. (b) Solution incompatibility may cause degradation of the allergenic extract. (c)Vigorous mixing has been reported to cause aggregation and particulates. (d) Some allergenic extracts are sensitive to silicone oil, which is frequently present in syringes and on syringe plunger stoppers.
Appendix 1 544	Each facility would conduct a microbial challenge study at least once for each mixed, diluted, or repackaged biological product, to demonstrate that the microbial quality of the biological product mixed, diluted, or repackaged by that facility can be ensured. *Add new text.*	**A bracketing approach utilizing the product that according to the literature might have the greatest growth promotion may be considered to reduce the number of individual challenge studies. Bracket study design utilizing the product having the greatest growth potential must also account for the range of sizes of the vial, or volume in the syringes, for the products included, such as the largest vial and the smallest fill volume.**	The requirement for at least one microbial challenge study for each mixed, diluted or repackaged product is excessive for the setting where a pharmacist prepares the product and then sends to the hospital floor for the patient. The need for 24 hours BUD in most hospital settings will be a minimum necessity, and the need to perform microbial challenges as described for each product would be an unreasonable burden, so long as the process, technique and system can be demonstrated to be robust through an appropriately designed bracketing approach. Such a bracketing approach should be risk based, and consider the product that would represent a worst-case due to its large size and growth-promoting properties. The other end of the bracket would consider the smallest

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			volume fill product, as that would represent the greatest number of aseptic manipulations from the bulk container to the final dosage form.
548 – 554	The challenge microbes should include the panel provided in USP<51> Antimicrobial Effectiveness Testing. These strains represent the species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus brasiliensis* (formerly Aspergillus *niger*). It should also incorporate typical skin microflora and nosocomial agents to simulate the types of flora that may contaminate a drug product in a healthcare setting. Finally, the challenge should include strains of the tribe *Klebsielleae*, as they have been shown to proliferate in infusion products.	The challenge microbes should include the panel provided in USP<51> Antimicrobial Effectiveness Testing. These strains represent the species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus brasiliensis* (formerly Aspergillus *niger*). **Other strains (e.g. from house flora) might be taken in consideration in the study design.**	FDA proposal is too limiting. PDA recommends that FDA allow for specific characteristics of the environment, where the activities are conducted.