American Academy of
Allergy Asthma & Immunology

May 20, 2015

To: Director, Center for Drug Evaluation and Research; and Director, Center for Biologics Evaluation and Research

Thank you for the opportunity to provide feedback on the draft guidance document entitled **"Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application"**. The American Academy of Allergy, Asthma and Immunology (AAAAI) is a premier specialty society representing more than 6,800 allergist-immunologists and related professionals worldwide dedicated to advancing allergy and immunology healthcare. The AAAAI would like to recognize the foresight of the FDA demonstrated by inclusion of section "III.C" dedicated to licensed allergenic extracts.

Our organization, on behalf of its membership, would like to take this opportunity to provide some additional suggestions for this guidance document. These comments are based on an extensive track record of safe allergenic extract preparation and administration by physician offices, pharmacies, federal facilities and industry. Comments are focused on this guidance document in recognition that other related documents recently posted defer to this one for biologics, and in particular allergen extracts.

We have identified the following themes that may require additional consideration before finalization of the guidance document (see Enclosure 1). We have also included a few specific language modification recommendations (see Enclosure 2).

Thank you again for the opportunity to provide feedback on this draft guidance document. This feedback is provided with complete understanding of the driving force behind the Drug Quality and Safety Act, and that our specialty and healthcare at large must continue to refine policies and practices in a manner that provides the safest and most efficacious care for patients. The AAAAI and our specialty remain committed to this goal.

Sincerely,

Robert F. Lemanske, Jr., MD, FAAAAI
President

2 Enclosures

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ENCLOSURE 1
Major Themes Deserving Additional Consideration

1. Use of custom mixes of FDA approved allergen extracts
    - Current allergen immunotherapy clinical practice often includes the use of custom mixes of FDA approved extracts by pharmacies, federal agencies and physician offices, and prescribing physicians to mix prescription treatment sets
    - Examples include grass pollen mixes and dust mite species mixes
    - This practice now will be considered repackaging (creation of a stock mixture) and subject to new licensing requirements or beyond use date requirements incompatible with clinical practice
    - Beyond use date for custom mixes should follow that of prescription treatment sets (earliest expiring component)
    - RECOMMENDATION: The ability to use a limited number of custom mixes meeting current practice parameter recommended mixing principles should be extended to state-licensed pharmacies, Federal facilities, outsourcing facilities, and physician offices under conditions specified in III.C. In addition, clarification as to what constitutes an outsourcing facility should be provided.
2. Beyond use dating for dilutions or reconstituted insect venom extracts
    - The ability to perform common standard practices of diluting patient treatment set vials or reconstituting insect venom lyophilized manufacturer supplied extracts should be extended to pharmacies, Federal facilities and physician practices if performed under conditions in III.C.
    - There is considerable confusion amongst practitioners as to whether current manufacturer licenses will be affected, and how this guidance in its current state will facilitate such practices
    - RECOMMENDATION: Sanction common dilution and reconstitution practices and apply beyond use date using same standard as for prescription treatment sets (earliest expiring component)
3. Use of allergen extracts across state lines and in other provider's offices
    - Some of our membership have indicated that the guidance as currently worded is unclear with respect to whether allergists can prepare extracts in their offices and transfer to another clinician for administration either within or across state lines
    - Misunderstanding by physicians with offices or referring providers across state lines may represent a barrier to care for patients
    - RECOMMENDATION: Clarification of intent by inserting a definition of transfer as clarification and consider deleting III.C.9 specifying distribution only to states in which preparer meets requirements since this is implied and represents a possible jurisdiction issue
4. Shared patient use of reconstituted insect venom extracts and possibly custom mixes
    - Clarification of whether single antigen or manufacturer supplied custom mixes (ready to use or requiring reconstitution such as insect venom extracts) can be used for multiple patients with individual prescriptions for that extract/mix
    - The use of reconstituted insect venom extracts for multiple patients is historically a common and safe practice (lack of reports of contamination or adverse events related to shared use practice yet admittedly not rigorously studied).
    - A minority of clinicians have also suggested that language be included to permit use of stock allergen extracts and custom mixes for shared patient use when prescribed for individual patients. This practice is not currently included in the most current immunotherapy practice parameter recommendations.
    - RECOMMENDATION: Insert language sanctioning shared patient use of single allergen or manufacturer supplied custom mixes, and consider shared patient use for custom mixes prepared by state-licensed pharmacy, Federal facility, outsourcing facility and physician offices under conditions specified in III.C.

ENCLOSURE 2
Language Modification Recommendations

Ref #	Line #	Recommendation	Comment
	436-437	Insert "or group of patients": "….licensed allergenic extracts would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient OR GROUP OF PATIENTS, even though…"	e.g. insect venom extracts This language suggested by one of our members or other language could be considered.
	452	Change physician to "physician office"	Consistent language in remainder of III.C and as worded restricts actual preparation to the provider and not clinic personnel as is most commonly practiced
	486	Insert "allergen extract section of" before USP….	Directs preparers to appropriate CSP reference of 2008
	491-493	Insert "An example of an acceptable transfer of a prescription set is from the physician office preparing the prescription set to another provider for regular administration." Between the two existing sentences	Clarify that a sale or transfer does not include administration of a prescription set in "ANOTHER" health care setting so that administration of immunotherapy at another provider's office (like a primary care physician) is not prohibited.
	495-496	Consider for deletion	See enclosure 1 comment
	500-514	1) Clarify primary and secondary labeling definitions 2) Consider secondary for II, III & IV 3) Clarify and standardize dilution expectation (e.g. use volume/volume)	1) Perhaps too much to fit on a 5ml vial 2) Space consideration unless primary labeling includes codes and attached paperwork/legend 3) v/v is the practice parameter recommendation; some may interpret this as the dilution for every component, whereas others may list the concentration of the dominant allergen component in the vial, others will unsuccessfully try to average (multiple units of components- BAU/ml, w/v, AU/ml, etc.)