ALLERGEN PRODUCTS MANUFACTURERS' ASSOCIATION

Industry Perspective from the Allergen Products Manufacturers' Association (APMA)

VRBPAC - 09 October 2025

Trena Repp, APMA president

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Introduction

- We want to thank Dr. Rabin for including the APMA in this discussion.
- Allergen products have been around since the early 1900s.
- Since then, knowledge about allergy and allergy treatments have grown, although there is still much to learn.
- Technology has also greatly advanced.
- The APMA agrees it is important to continue to innovate and improve our products to provide the best treatments to the allergic patient.

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The initiatives as the APMA understands them

- To discontinue the current BAUs and use mass concentrations of major allergens in conjunction with the change of the Cat and Ragweed RIDs to ELISA, which are already in progress.
- To use the Cat/Ragweed ELISA implementation model to standardize additional products, such as food allergens.
- To use LC-MS for release of complex allergen extracts, starting with house dust mite extracts. This would be combined with the use of individual allergen assays like Der p 1 and Der p 2 ELISAs.
- To add fecal pellets to the current mite body extracts to better cover the patient allergic response.

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BAUs to major allergen for cat and ragweed – clinical link

- The decision to use BAUs in the US for standardized products was made in the early 1990s
  - BAUs were developed based on skin testing, using the intradermal dilution for 50 mm sum of erythema ($ID_{50}EAL$) to linking BAUs to a clinical response.
  - There was a desire to limit the number of units in allergen products to reduce errors in patient administration.
- It is the position of the APMA to have a clear link of the major allergen mass concentration to the BAUs when changing the Cat and Ragweed units.
  - Maintains the link to skin testing.
  - Provides a conversion for allergists when adopting the new units in the clinical setting.

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BAUs to major allergen - labelling

- Currently, an extract with the range of 10-20 Fel d 1 units/mL is labelled as a 10,000 BAU/mL Cat extract.
- The APMA perspective is to label major allergens in the same manner as BAU labelling, and not to report the individual batch results.
  - Theoretical example: If directly converting BAUs to major allergen concentration, all extracts with a range of 40 – 80 Fel d 1 µg/mL would be labelled as “60 µg/mL Fel d 1 protein.”
- Accounts for method variability.
- Consistent with current BAU labelling.
- Discourages unnecessary discrimination in individual batch selection at the clinic.

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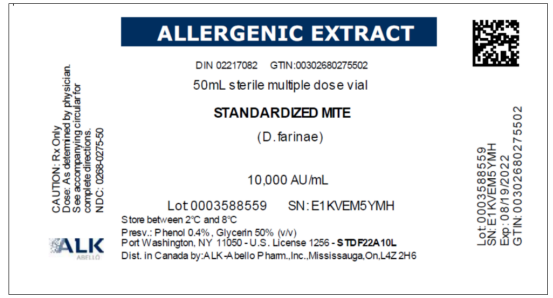
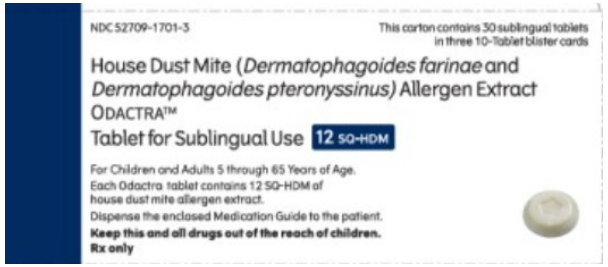
LC-MS - Mites

- Current approved house dust mite products are very diverse in manufacturing processes, matrix, and route of administration
  - Bulk extracts of house dust mite bodies used for SCIT and skin testing.
    - Three manufacturers with different processes.
    - Backed by decades of real-world use.
  - SLIT tablets from house dust mite body and house dust mite fecal extracts with specified ratios of four major allergens
    - Different processes than the bulk extracts.
    - Backed by clinical data and years of real-world use.





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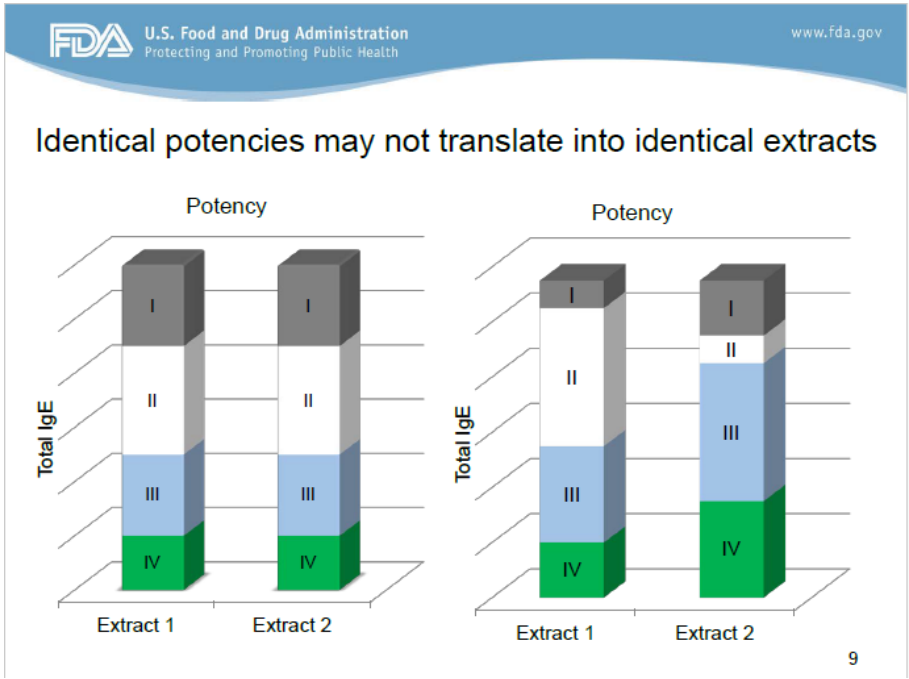
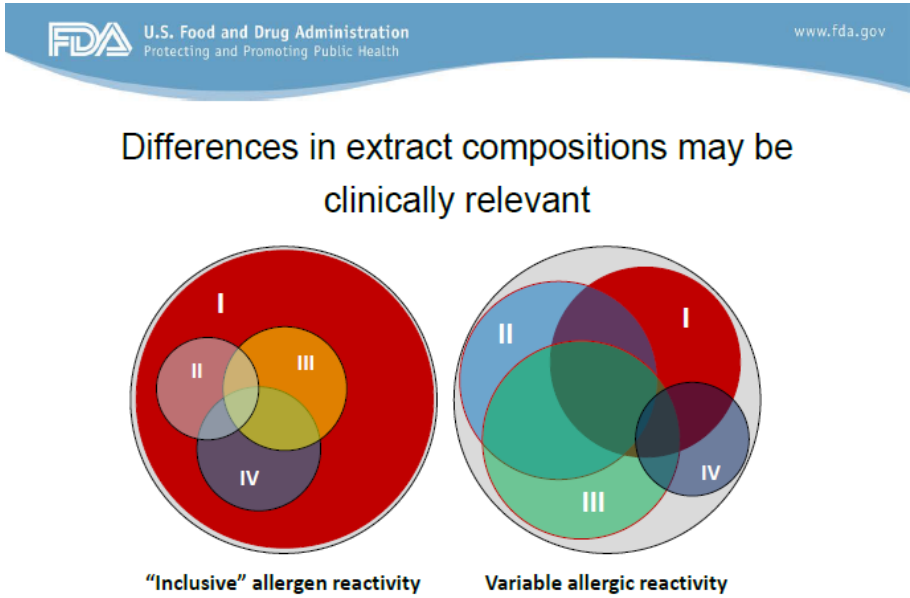
LC-MS - concerns

- It is not clear to the APMA how LC-MS will be implemented
- The current house dust mite products may not be identical in composition and MS profile.
  - All are approved and have a history of safe and effective use.
  - Some are supported by clinical trials.
- A single standard may not be applicable to all current house dust mite products.
  - The selection of the standard is critical to the method and conformance to the standard can be influenced by the extraction process.
- MS equipment is expensive, and industry experience is limited.
- Current batch to batch variability is not known.





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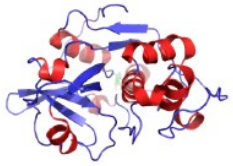
LC-MS

- The APMA perspective is, if implemented,
  - LC-MS
    - Used to detect and identify the major and minor allergens present and to characterize and demonstrate consistency, but not for routine release testing.
    - Evaluated retrospectively for current products
    - Evaluated during development for any future products
  - Immunochemistry methods, whether it be the RP ELISA or new multiple major allergen ELISAs.
    - Used for batch release to confirm the LC-MS data and demonstrate consistency of the extracts.

LC-MS/MS characterization of house dust mite extracts

Allergène groupe	*D. farinae*			*D. pteronyssinus*		
	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5	Lot 6
1	✓	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓	✓
4	✓	✓	✓	✓	✓	✓
6	✓	✓	✓	✓	✓	✓
8	✓	✓	✓	✓	✓	✓
9	✓	✓	✓	✓	✓	✓
11	-	-	-	✓	✓	✓
14	✓	✓	✓	✓	✓	✓
15	✓	✓	✓	✓	✓	✓
18	✓	✓	✓	✓	✓	✓
22	✓	✓	✓	-	-	-
23	-	-	-	✓	✓	✓
25	✓	✓	✓	✓	✓	✓
26	✓	✓	✓	✓	✓	✓
27	✓	✓	✓	✓	✓	✓
30	✓	✓	✓	✓	✓	✓



Der p 1

Der p 2

✓ Detection / identification during process validation of major and minor allergens.

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12 ALK company presentation ALK

Pro and Con

Assay	Pro	Con
Immunoassay: ELISA, RID, CIE	• Current standard • Stability indicating	• Isoform coverage may not be detected and quantified • Supply of Abs
MS	• High specificity • High sensitivity • Multiplexing for quantification	• Cost (DKK 4-6M) • Specialized FTEs (1-2) • Not stability indicating

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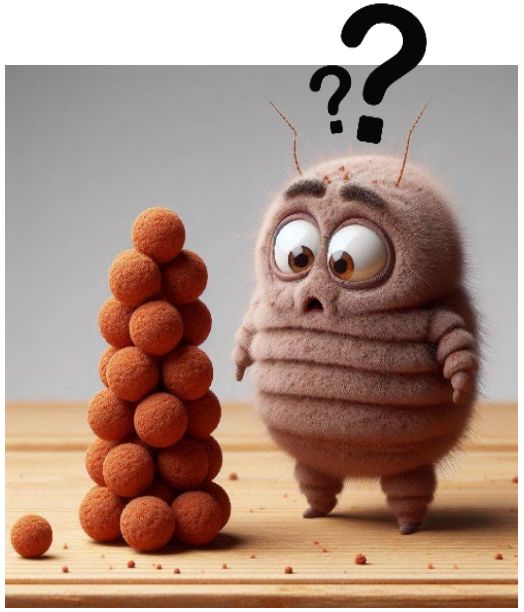
Addition of house dust mite fecal to extracts

The APMA perspective is that current products already contain fecal allergens

- Current house dust mite body extracts
  - The extracts do contain fecal material and fecal related major allergens. These are made available for extraction through grinding of the bodies prior to extraction.
- The house dust mite SLIT tablet contains both body and fecal extracts, with defined ratios of mite major allergens
  - ALK holds US and global patents on the source material, drug substance, and drug product processes for creating a drug product with defined ratios of house dust mite Der 1 and Der 2 major allergens. US9265824B2.



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New Standardized Products

- The APMA supports innovation and modernization of allergen products in ways that benefit the patient.
- Global standardization initiatives
  - Most manufacturers have the same products approved in markets outside of the US, some of which have their own standardization initiatives.
  - We are concerned that if multiple standards are created worldwide for the same allergen, it will be costly to demonstrate conformance to all standards and may not be possible.
- Cost considerations for the clinics and patients
  - Standardized products are more costly to produce.
  - Will the doctors accept the additional costs?
  - Has there been a cost/benefit analysis performed for the patients?
- Will CBER accept alternate methods, if a BLA holder can demonstrate it is an appropriate alternate to the CBER method?

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New Standardized Products - Foods

- Standards for food may be complicated
- The route of administration and drug product formulations are very different across food allergy drugs that are approved and in clinical trials.
  - Current skin test diagnostics
    - Bulk extracts
  - New approved therapies
    - Oral Immunotherapy
  - Examples of novel food therapies in clinical development
    - Epicutaneous immunotherapy
    - Sublingual Immunotherapy Tablets
    - Peptide mixtures
- Food immunotherapy products are new products backed by Clinical Trials, is standardization necessary?

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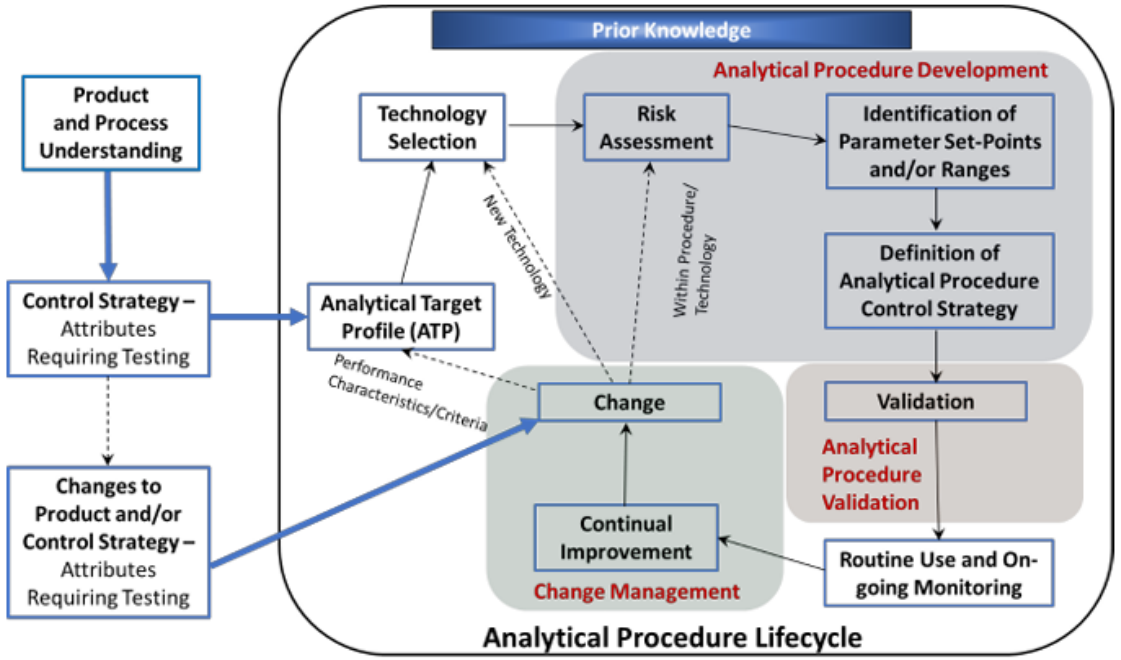
General method considerations

- ICH Q14 Analytical Procedure Development provides relevant principles for analytical method lifecycle management.
  - Will these principles be applied to the creation of new methods and standards?
- Not every product matrix will work with every standardized method.
- Consider ring trials with the manufacturers before implementation.

Figure 1: The analytical procedure lifecycle



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Impact to current BLAs

The APMA would like the agency to be aware of the impact of these changes to current BLAs

- Changes to product labelling, requiring many labelling system changes
- PI updates
- SPL submissions
- NDC/GTIN updates

The APMA would like to request the agency consider a defined path for changes directly resulting from these initiatives to better utilize time and resources of industry and CBER.

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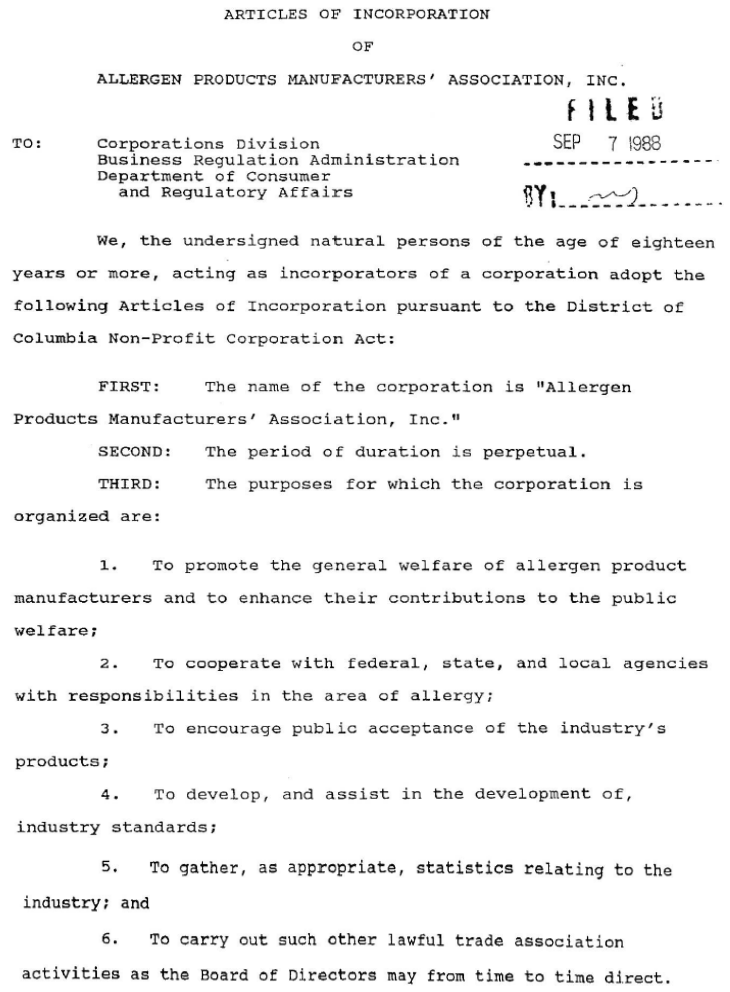
CBER/APMA collaboration

- Since incorporation in 1988, the purpose of the APMA has been:
  - To promote the general welfare of allergen product manufacturers and to enhance their contributions to the public welfare;
  - To cooperate with federal, state and local agencies with responsibilities in the area of allergy;
  - To encourage public acceptance of the industry's products;
  - To develop and assist in the development of, industry standards;
  - To gather, as appropriate, statistics relating to the industry; and
  - To carry out such other lawful trade association activities as the Board of Directors may from time to time direct.
- For over 35 years, CBER and the APMA have maintained this collaboration.
- We look forward to continued collaboration with CBER on these new initiatives.



ARTICLES OF INCORPORATION

OF

ALLERGEN PRODUCTS MANUFACTURERS' ASSOCIATION, INC.

FILED

SEP 7 1988

BY:

TO: Corporations Division
Business Regulation Administration
Department of Consumer
and Regulatory Affairs

We, the undersigned natural persons of the age of eighteen years or more, acting as incorporators of a corporation adopt the following Articles of Incorporation pursuant to the District of Columbia Non-Profit Corporation Act:

FIRST: The name of the corporation is "Allergen Products Manufacturers' Association, Inc."

SECOND: The period of duration is perpetual.

THIRD: The purposes for which the corporation is organized are:

1. To promote the general welfare of allergen product manufacturers and to enhance their contributions to the public welfare;

2. To cooperate with federal, state, and local agencies with responsibilities in the area of allergy;

3. To encourage public acceptance of the industry's products;

4. To develop, and assist in the development of, industry standards;

5. To gather, as appropriate, statistics relating to the industry; and

6. To carry out such other lawful trade association activities as the Board of Directors may from time to time direct.

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Thank you!

Questions?