

# Validation of Cleaning Systems: Allergens

3-A SSI 2015 Education Conference  
The Bridge to Hygienic Design  
Tuesday, May 12 2015

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**The food of one may be  
poison for another.**

Lucretius

*De Rerum Natura*

# Food Allergies

Between **3.5-4%** of the U.S. population (or **10-14 million Americans**) have food allergy

Prevalence of food allergy is **increasing**

*Sicherer, et al. J. Allergy Clin Immunol. 1999;103:559-62.*

*Sicherer, et al. J. Allergy Clin. Immunol. 2004;114:159-165.*

# Food Sensitivities:

Individualistic Adverse Reactions to Foods

## Food Allergies

*(Immune mediated)*

IgE-Mediated

True Food Allergy  
*Immediate*

Cell-Mediated

Celiac Disease  
*Delayed*

## Food Intolerances

*(Non-immune mediated)*

Lactose  
Intolerance



# CELL-MEDIATED FOOD ALLERGIES

## Delayed Hypersensitivity

# Celiac Disease

- Affects least 1 per 2000 in U.S. but could be much higher (1 per 133) -3 million Americans-
- Associated with consumption of **gluten** fractions of **wheat, rye, barley**, triticale, and sometimes oats
- **Delayed hypersensitivity reaction** with symptoms developing 24-72 hrs after ingestion
- T cell-mediated inflammatory response in small intestine
- Small intestine loses its absorptive capacity → body wasting, anemia, diarrhea, bone pain, etc.
- Treatment with avoidance diets



# Celiac Disease Effects on Small Intestine

**Healthy Small Intestine Biopsy**



**Celiac Small Intestine Biopsy**





# IGE-MEDIATED FOOD ALLERGIES

Immediate Hypersensitivity



# IgE-Mediated Food Allergies

- “True” food allergies
- Antibodies against food allergens (proteins)
- Two phases in IgE-mediated allergy mechanism
  1. Sensitization
  2. Mediator release and reaction

# Typical Symptoms of IgE-Mediated Reactions to Foods

## Gastrointestinal

- Nausea
- Vomiting
- Abdominal pain
- Diarrhea

## Cutaneous

- Urticaria (hives)
- Angioedema (swelling)
- Atopic dermatitis (eczema)

## Respiratory

- Rhinitis (runny nose)
- Laryngeal edema (throat swelling)
- Asthma

## Systemic

- Anaphylactic shock

# Food-Induced Anaphylaxis is *Not* a Rare Occurrence

Researchers estimate **29,000 emergency room visits and 150-200 deaths per year** due to food-induced anaphylaxis (U.S.)

*Bock et al. J. Allergy Clin. Immunol. 2001;107:191-193.*

# Most Common Causes of IgE-Mediated Food Allergy

## “The Big 8”



Cows' milk



Egg



Crustacea



Fish

Peanut



Soybean



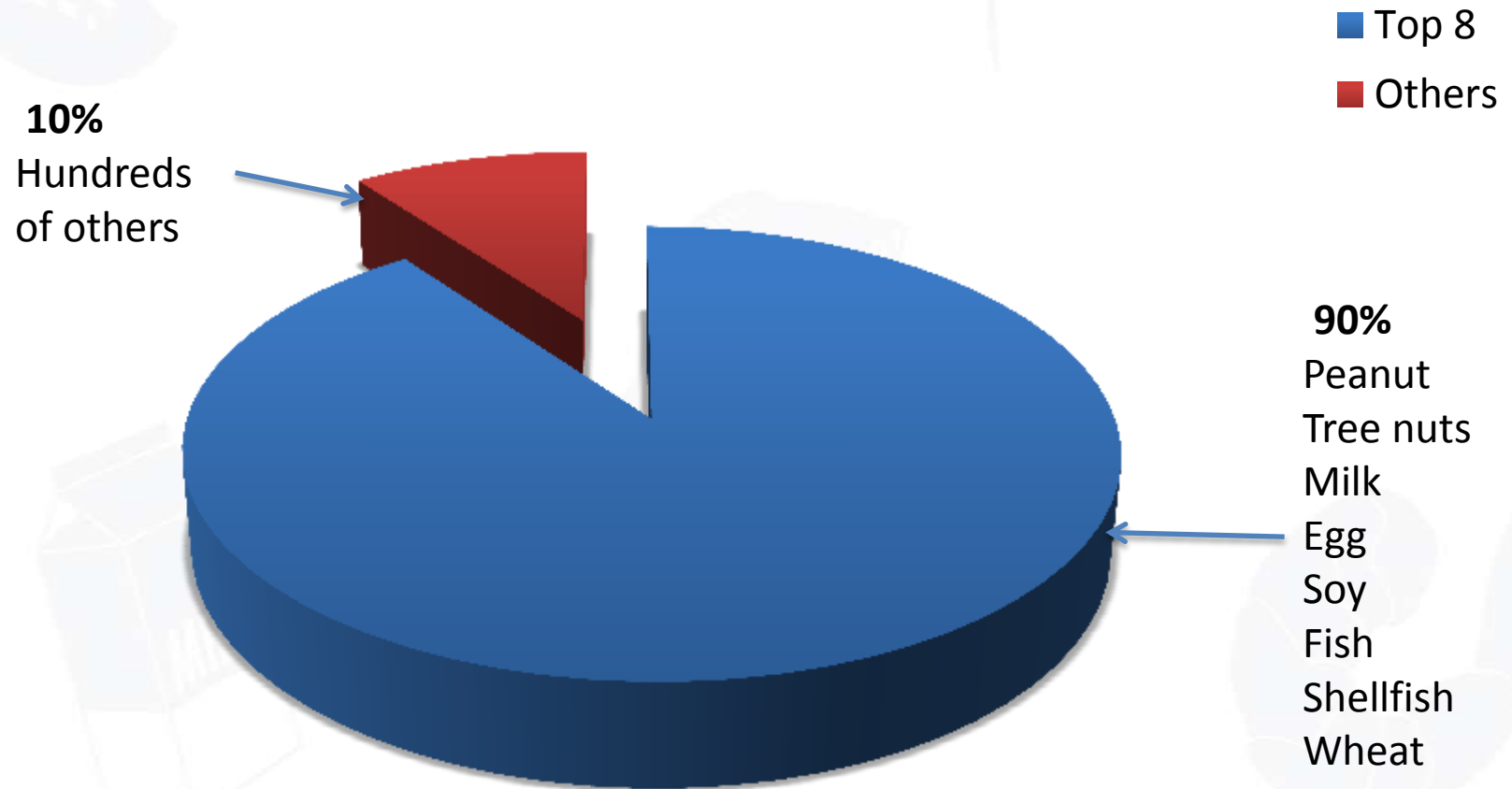
Tree nuts



Wheat



# Food Allergies Prevalence



# Causative Agents of Food Allergies

- Naturally-occurring **proteins**
- Heat-resistant
- Resistant to proteolysis
- Resistant to extremes in pH
- Usually major proteins of the food
- Foods can have 1 or many allergens in them

# Treatment for True Food Allergies

## Specific Avoidance Diets

### Potential issues

- Degree of selectivity
- Knowledge of food composition
- Adequate nutrition
- Restaurant meals
- Confusing labeling terms
- Exquisite sensitivity

**How much is too much?**

**Milligram amounts!**  
(ppm concentrations)

# Food Allergen Labeling & Consumer Protection Act of 2004 (FALCPA)

- Defined major allergen sources as 8 foods/food groups (the Big 8)
  1. Egg
  2. Milk
  3. Fish
  4. Crustacean shellfish
  5. Peanuts
  6. Tree nuts
  7. Soybeans
  8. Wheat
- Presence of the major food allergens, or ingredients that contain protein from these foods *must be declared on the label* of FDA-regulated products



# FALCPA

- Plain English must be used, for example:
  - “Milk” must be used for whey or casein ingredients
  - “Wheat” must be specified for flour
- Two labeling options
  - Ingredients list
  - Contains statement

## Ingredients List

**Ingredients:** Enriched flour (wheat flour, malted barley, niacin, reduced iron, thiamin mononitrate, riboflavin, folic acid), sugar, partially hydrogenated cottonseed oil, high fructose corn syrup, whey (milk), eggs, vanilla, natural and artificial flavoring, salt, leavening (sodium acid pyrophosphate, monocalcium phosphate), lecithin (soy), mono- and diglycerides.

## Contains Statement

**Ingredients:** Enriched flour (wheat flour, malted barley, niacin, reduced iron, thiamin mononitrate, riboflavin, folic acid), sugar, partially hydrogenated cottonseed oil, high fructose corn syrup, whey, eggs, vanilla, natural and artificial flavoring, salt, leavening (sodium acid pyrophosphate, monocalcium phosphate), lecithin, mono- and diglycerides.

**Contains:** Wheat, Milk, Egg and Soy.

FDA. *Guidance for Industry: A Food Labeling Guide*

<http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM265446.pdf>

# FALCPA

- Must specify the type of tree nut, and species of fish or crustacean shellfish
- Labeling exemptions
  - Highly refined oils
  - Petitions for exemption
- Voluntary precautionary/advisory labeling
  - “May contain” statements
  - **Cannot** be used as a substitute for good manufacturing practices

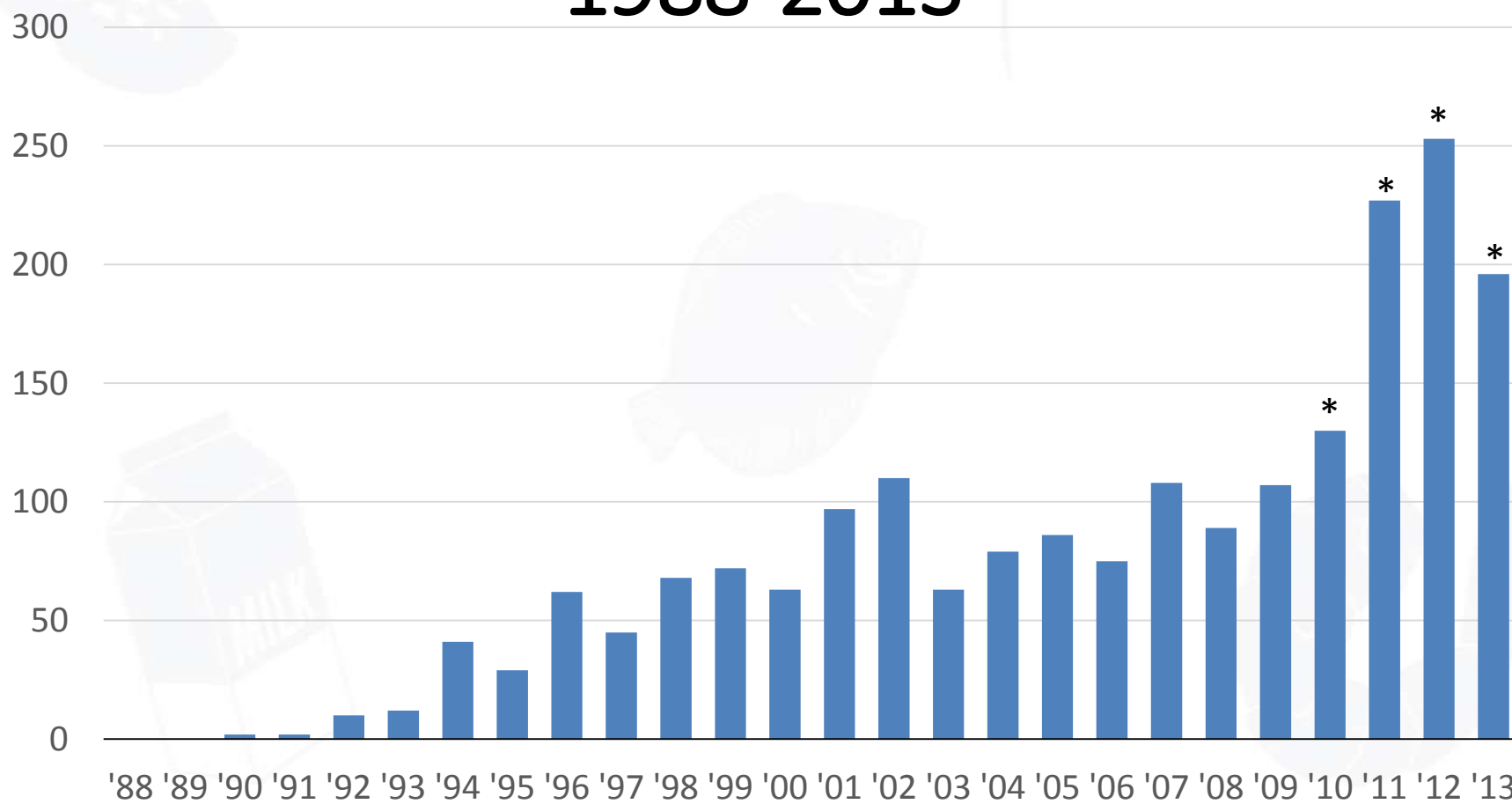
# FDA Gluten-Free Labeling Rule

- Gluten-containing grain
  - Wheat
  - Rye
  - Barley
  - Or crossbred hybrids
- Foods labeled as “gluten-free” may not contain:
  - An ingredient that is a gluten-containing grain
  - An ingredient derived from gluten-containing grain, if it has not been processed to remove gluten
- **Finished product must contain < 20 ppm gluten**

# Recalls

Reportable Food Registry lists *undeclared allergens as the leading cause of U.S. recalls*

# U.S. FDA Food Allergen Recall Incidents 1988-2013



\* Includes FDA recalls & alerts

# Food Allergies

- Food allergies: immune-mediated sensitivities
- Food allergens: naturally-occurring proteins in foods
- ***Importance of food allergens to the industry***
  - Health risk
  - Regulatory risk
  - Business Risk



# EFFECTIVE ALLERGEN CONTROL PLANS



# Essentials of Allergen Control

- Form an allergen control team
- Conduct a quantitative risk assessment to determine the extent of the concern
- Develop an allergen process flow diagram (allergen map)
- Develop an allergen control plan (ACP) specific to each processing facility and each product
- Review the ACP on some regular basis and especially for new products, introduction of new processing capabilities, new ingredients

# Where Risks Occur

- Research and Development
- Engineering and System Design
- Raw Materials/Suppliers/Co-Packers/Purchasing
- Labeling and Packaging
- Production Scheduling/Changeovers
- Rework
- Sanitation
- Human Error

# Keys to Effective Allergen Control

- Dedicate – facility, system, line, etc.
- Segregate
- Separate
- Sanitize



# Example Processing Errors/Oversights

- Inadequate cleaning of shared equipment
- Use of re-work
- Switching of ingredients
- Formulation mistakes
- Wrong labels/packages
- Labeling terms

# Common Allergen Control Plan Gaps

- Inadequate packaging controls
- Lack of documentation on effectiveness of allergen control plan
- Use of advisory labeling as a substitute for Good Manufacturing Practices
- Inadequate knowledge of suppliers and associated allergen risks
- Lack of internal standards
- Poor choices of analytical methods for documentation

# Allergen Detection Methods

- Enzyme-linked Immunosorbent Assay (ELISA)
  - Antibody based methods
  - Detects protein
  - Qualitative: Lateral flow devices (LFD)
  - Quantitative
- PCR
  - Detects DNA
- Mass Spectrometry

# Allergen Detection Methods

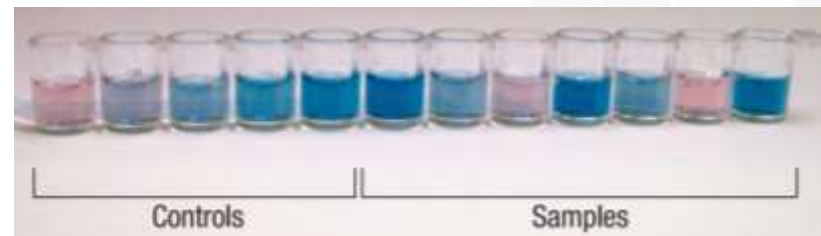
## Qualitative Methods (LFDs)

- Fast- results in minutes
- Easy- can be run in the plant
- Works well with swabs and rinse waters
- Positive or negative answer
- Limited use with finished product or ingredients



## Quantitative Methods

- Longer running time
- Requires training
- Provides quantitative results, typically in parts per million (ppm) of allergenic food
- Used regularly with finished product and ingredients



# Allergen Control Plan Validation: The FARRP Approach

1. Know Your Allergens
2. Develop SSOPs
3. Validate the SSOPs
4. Re-Validate the SSOPs
5. Validate Overall ACP



# The FARRP Approach

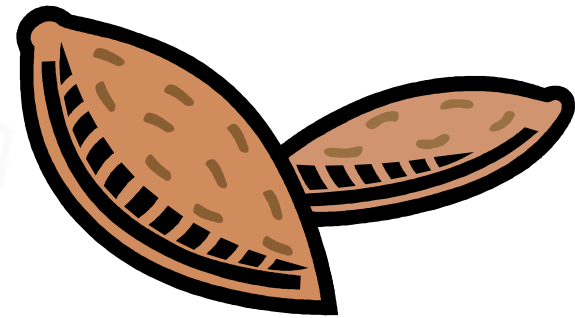
- Step 1 – ***Know Your Allergens***
  - Allergen load is extremely important; focus on allergenic ingredients of highest protein load
  - Allergen form is also important
    - Particulate vs. non-particulate
    - Liquid, dry, powder, paste, etc.

# Allergen Load

- Some ingredients contain **high** level of allergenic protein, for example
  - Casein
  - Gluten
  - Soy flour
- Other ingredients contain **modest** level of allergenic protein, e.g.
  - Lactose
- Some ingredients contain **low to very low** level of allergenic protein, e.g.
  - Soy lecithin
  - Fish oil
  - Butter

# Allergen Composition

- Almond Pieces?
- Almond Powder?
- Almond Butter?



❖ Consider:

Difficulty to clean and potential risk factors.

How much equipment will be exposed?

# The FARRP Approach

- Step 2 – ***Develop SSOP for each line and each allergenic ingredient***
  - If several ingredients have similar form (dry powders) then you can assume that cleaning is equivalent
  - If several lines have identical set-ups, then same SSOP should work for all
  - Focus on allergenic ingredients of highest protein load
  - But may need some evidence that this is right choice

# SSOP Development: Wet Cleaning

- Wet cleaning is the best option but not always possible
  - Allergens tend to be water-soluble
  - CIP systems can be operated very consistently
  - Easy to document CIP systems
  - Final rinse water is very dilute but allows simple documentation of effectiveness of cleaning

# SSOP Development: Dry Cleaning

- Dry cleaning can be difficult for many reasons
  - Nature of the allergen load
    - Sticky such as peanut butter or chocolate
    - Particulate
    - Inconsistent distribution
    - High, low, intermediate
  - Approaches harder to consistently apply
    - Vacuuming is probably best
    - Scraping, brushing
    - Wet or alcohol wipes
  - Inaccessible areas of equipment
    - May require retrofitting for accessibility

# SSOP Development: Dry Cleaning

- Push through is another common approach to dry cleaning
- Works well with powders, particulates but not with sticky or viscous materials
- Use non-allergen formulation or inert substance (salt, sugar, flour, etc.)
- Determine amount of push through with quantitative ELISA tests; need amount to achieve corporate target level; validate x2 in trials before production begins
- Each facility may be different with push-thru volume

# The FARRP Approach

- Step 3 – ***Validate the SSOP for each line***
  - But perhaps not every allergenic ingredient
  - Be prepared to make a good argument for selection of testing one allergen but not others
  - Be really careful about skipping analysis for minor ingredient that is highly allergenic, e.g. peanut
  - Minor allergenic ingredients e.g. soy lecithin can be ignored based on calculations, expert opinion letters



# The FARRP Approach

- Step 3 – ***Validate the SSOP for each line***
  - Run the allergenic formulation
  - Test the dirty equipment (positive control)
  - Do the SSOP
  - Perform allergen-specific ELISA swabs/lateral flow strips on equipment surfaces, CIP rinse water, etc. (multiple swabs are advised)
  - If non-detect, you pass and can run next product
  - If allergen detected, more cleaning is needed

# The FARRP Approach

- Step 3 – ***Validate the SSOP for each line***
  - Repeat the whole cycle again
  - If you get non-detect on two successive runs, then you have a validated SSOP
  - Develop an approach to determine that SSOP is performed each time
  - Not necessary to do allergen swabs each time once validation is complete

# The FARRP Approach

- Step 3 – ***Validate the SSOP for each line***
  - Can use allergen swabs to validate that visually clean, ATP, or general protein is a sufficient approach
  - Can use ATP as a first pass assessment; if ATP is positive, then allergen swab will be positive

# SSOP Validation: Dry Cleaning

- Because results are likely to be more inconsistent, the number of tests to confirm cleaning effectiveness is increased (swabs and finished product)
- Try to find the most difficult-to-clean places in the equipment and swab those
- Use swabs to identify areas that may require extra cleaning efforts
- Use COP where possible on areas where disassembly is possible
- Use CIP in specific areas if possible

# The FARRP Approach

- Step 4 – ***Re-Validate the SSOP***

- Re-validate periodically using allergen swabs; frequency is not fixed
- Re-validate when anything changes
  - Formulation
  - Equipment
  - Matrix
  - processing conditions
  - SSOP parameters
  - allergen test kit
- Keep records of all test results

# The FARRP Approach

- Step 5 – ***Validate Overall ACP***
  - When you are 99.9% sure that you will get BLQ result, do finished product testing by quantitative ELISA – this is the ultimate assessment
  - Repeat finished product testing periodically



# FUTURE DIRECTIONS FOR ACP VALIDATION

# The Current Situation

- Many food manufacturers rely primarily on visually clean as the standard for allergen clean
- When testing is done to validate ACP or SSOP, the most popular approaches are ATP and general protein
- Among allergen-specific test methods, ELISA is the most popular – specific and sensitive
- Qualitative ELISA are especially popular – swabs and lateral flow strips



# Analytical Gaps

- Visually clean is hard to standardize; will FDA continue to accept it?
- ATP and general protein tests are not as sensitive or as specific as ELISA
- ELISA test methods are not standardized or validated
- ELISA – reference standards do not exist and calibration units vary
- ELISA – processing can affect results
- Two different ELISAs for the same allergen may yield different results

# FARRP Prediction of the Future - Analytical

- Food Safety Modernization Act (FSMA) implementation will start with general requirements but get more specific
- Visually clean will continue to be used but only with analytical verification
- Analytical testing by the food industry will grow to meet requirements for FSMA validation of ACPs
- ELISA will continue as the method of choice because of ruggedness
- ELISA users will become increasingly frustrated by the lack of standardization

# FARRP Prediction of the Future - Analytical

- Even more convenient test formats will be developed – speed, cost, ruggedness
- Multiplex methods will have a place but only if you can select your analytes
- Confirmation of test results will primarily be a regulatory issue
- Mass spec will increasingly become a good confirmatory method

# Allergen Control

- Effective Allergen Control Plans
  - Consider risks throughout development and production
  - Specific to each facility and each product
- Allergen Control Plan Validation
  1. Know Your Allergens
  2. Develop SSOPs
  3. Validate the SSOPs
  4. Re-Validate the SSOPs
  5. Validate Overall ACP
- Detection Methods for Validation
  - Allergen-specific methods for validation (ELISA)
  - Surrogate methods for routine verification



[www.farrp.org](http://www.farrp.org)

Thank you!