Overview of FDA Consultations

Specialty Crop
Regulatory Assistance Workshop
December 6-8, 2011

Robert I. Merker, Ph.D.
Supervisory Consumer Safety Officer
FDA/Center for Food Safety and Applied Nutrition
Division of Biotechnology and GRAS Notice Review
robert.merker@fda.hhs.gov

FDA's Regulation of New Plant Varieties

- 1986 – Coordinated Framework
  - Use of existing legal framework for ensuring safety of products of biotechnology
- 1992 – FDA's Statement of Policy on Foods Derived from New Plant Varieties
  - Utilize existing provisions of Federal Food, Drug, and Cosmetic Act (FD&C Act) for ensuring the safety of food from New Plant Varieties including those produced using recombinant DNA methods

1992 Policy Considerations

- Is the bioengineered food as safe as conventional food
- FD&C Act, Section 402: Adulteration: Unintended levels of toxicants present due to breeding or unintended effects of insertion of new genes
- FD&C Act, Section 403: Misbranding: labeling must be truthful and not misleading

1992 Policy Considerations

- Are new proteins unsafe Food Additives?
  - The FD&C Act: Section 409
  - New proteins in food could be food additives if they are not generally recognized as safe (GRAS)
  - Precedent set with FLAVR SAVR tomato
    - 21 CFR § 173.170 aminoglycoside 3'-phosphotransferase II – only approved food additive, reviewed by request of petitioner (a.k.a. NPT II, neomycin, kanamycin resistance element from *Escherichia coli*)

GRAS in a Nutshell

- Reasonable certainty of no harm (under conditions of use in food)
- Information supporting safety is publicly available and widely accepted.
- FDA views DNA as GRAS – we eat it.

Guidance in 1992 Policy

- Provides flowcharts for scenarios of traits that might be used
- Advises consultation with agency, early and often

FDA's Regulatory Programs

3 Regulatory Programs for Food Derived from New Plant Varieties

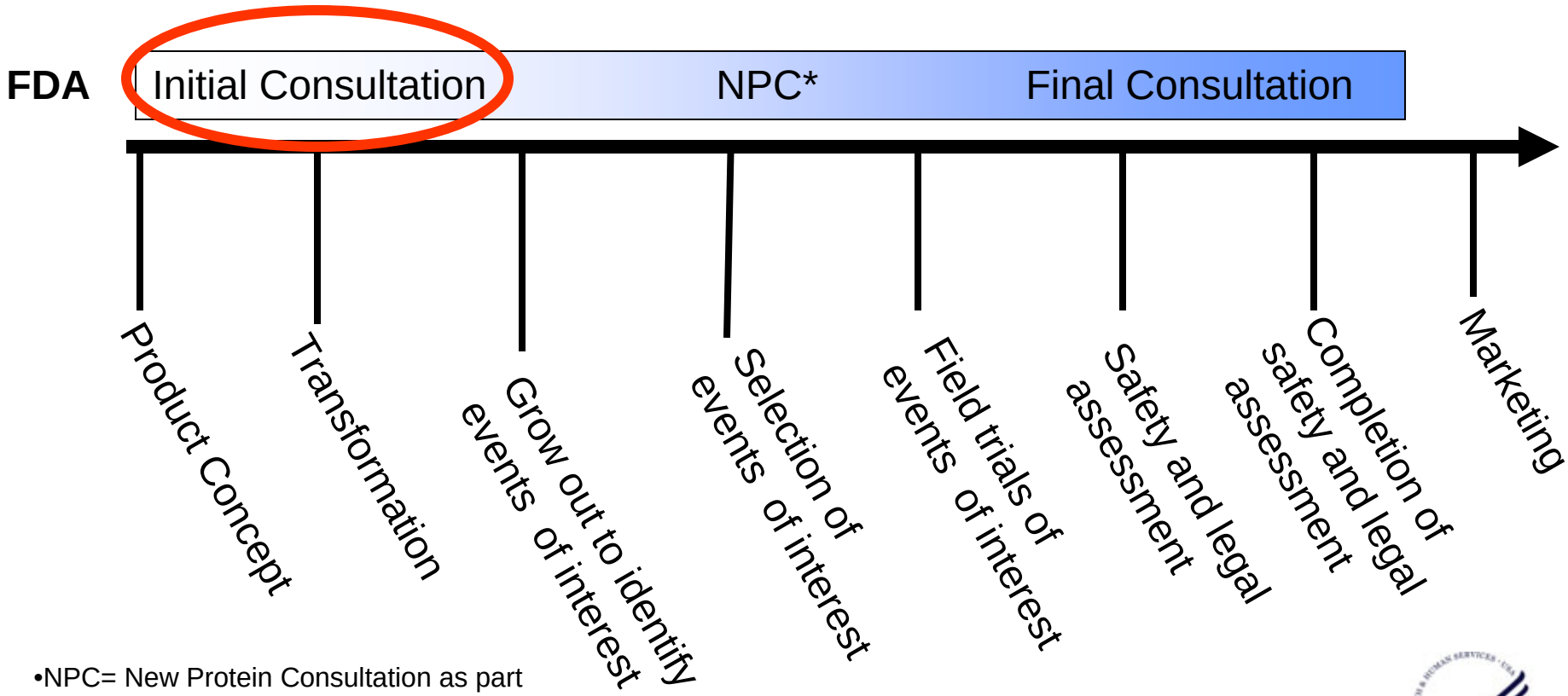
1. Initial Consultation
2. Early Food Safety Assessment (New Protein Consultation)
3. Final Consultation

- You can participate in these programs free of charge
- You may communicate with FDA in person, by phone, email, or mail.

- Your participation in these programs can help you ensure that foods from your new GE varieties will meet safety and legal requirements early in the development process and prior to marketing.

- FDA encourages consultation with the agency early and often

Navigating FDA's Regulatory System



•NPC= New Protein Consultation as part of FDA's early food safety assessment program for new, non-pesticidal proteins

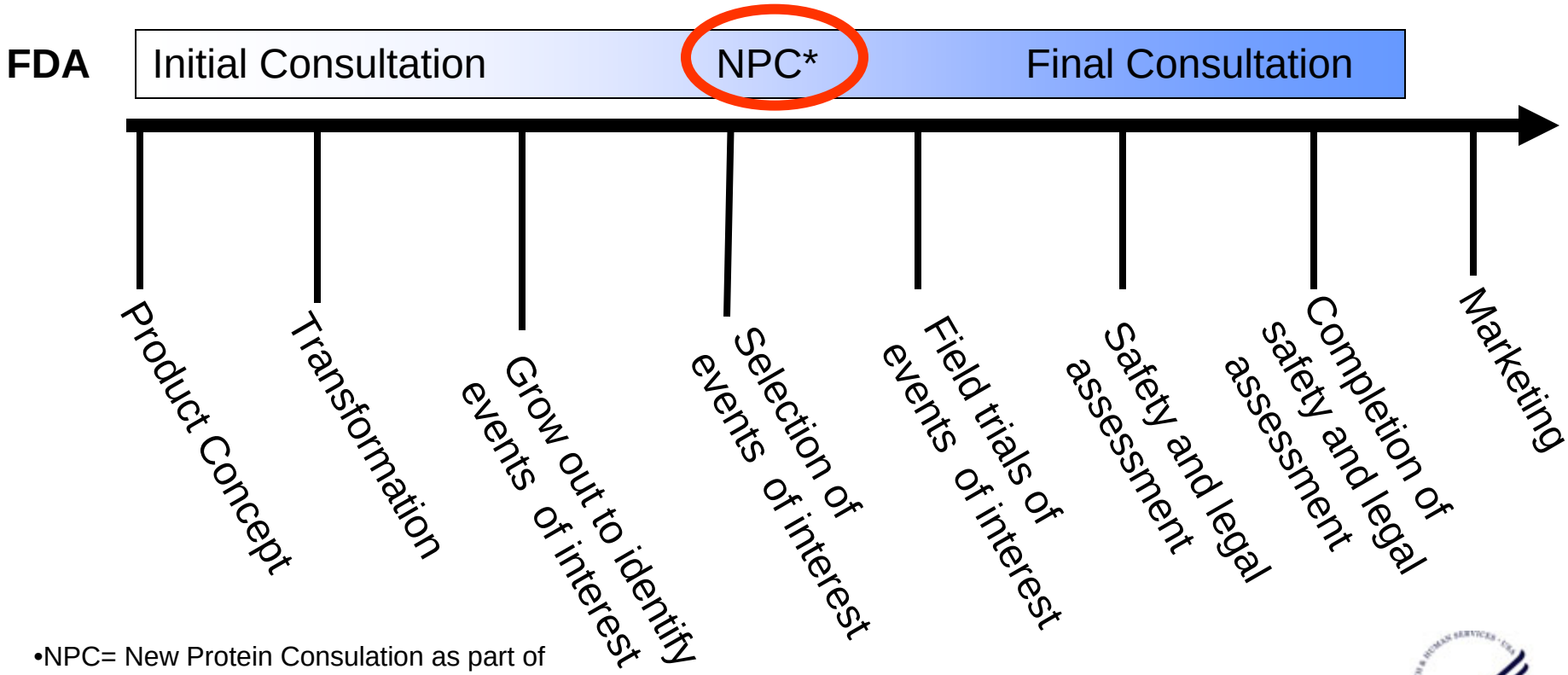
The Initial Consultation

- May occur very early in product development with continued contact afterward as needed
- Generally starts as a discussion between FDA and the developer
- Opportunity to identify likely safety and regulatory issues early in the development process, making the regulatory process more predictable. Allows for early feedback from FDA,
- May enable developers to make informed decisions regarding the difficulties of bringing a variety to market.
- Developers may consult with FDA based only on preliminary data

On FDA's Website

- Guidance "Guidance on Consultation Procedures Foods Derived From New Plant Varieties" http://www.fda.gov/bioconprocguidance

Navigating FDA's Regulatory Programs



•NPC= New Protein Consulation as part of FDA's early food safety assessment program for new, non-pesticidal proteins

Early Food Safety Assessment (New Protein Consultation)

- Enables developers to ensure that new, non-pesticidal proteins in bioengineered crops under development are neither toxic nor allergenic prior to any inadvertent presence of a crop containing the protein in the food supply
- A bioinformatic approach. Comparison of protein sequence to sequences of known protein toxins and allergens
- Firms submit to FDA an assessment of the potential toxicity and allergencity of the new protein
- Evaluation focuses on the safety of the protein, not on the use of the protein in a specific crop

Early Food Safety Assessment (New Protein Consultation)

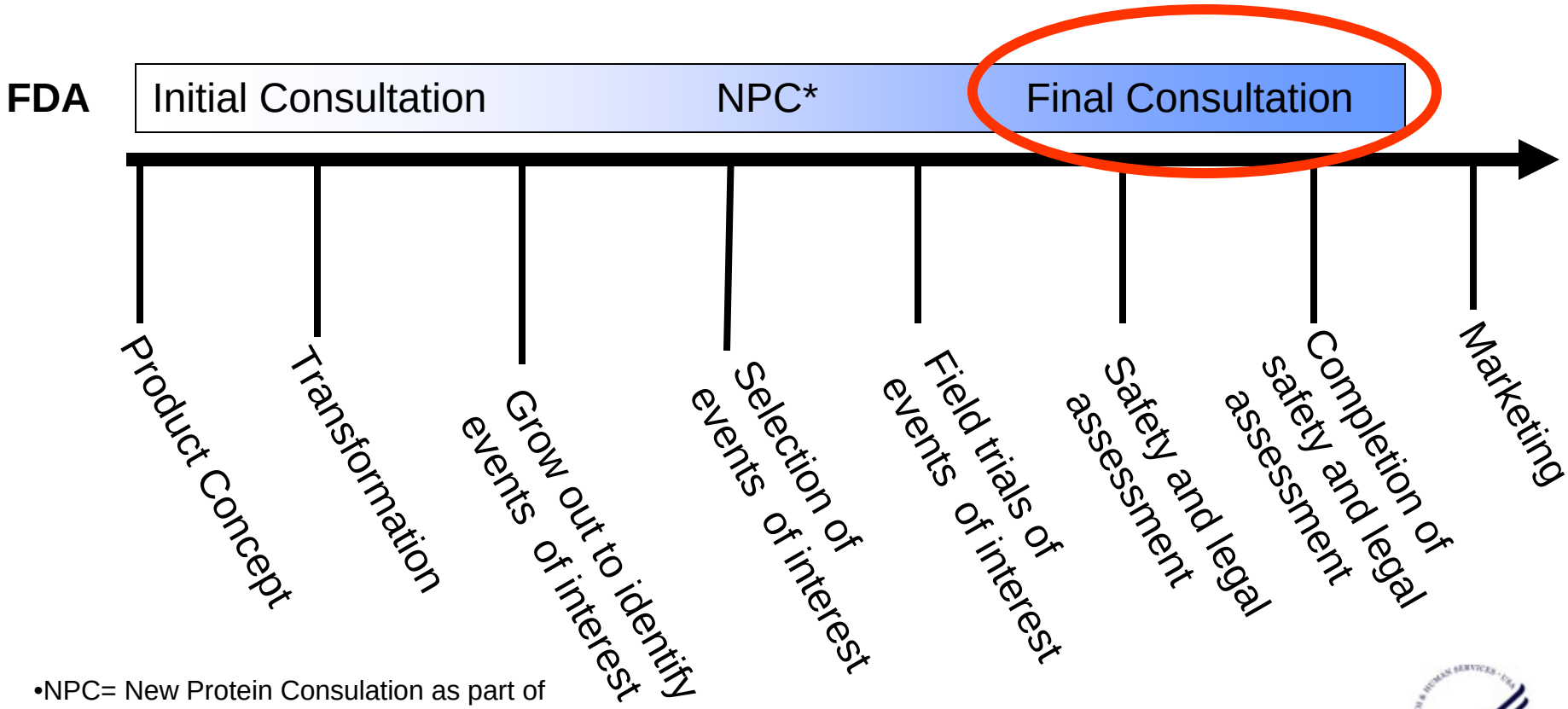
- Does not apply if new proteins are pesticidal; such proteins are under EPA purview.
- For non-pesticidal proteins not previously evaluated by FDA, the early food safety evaluation program would apply.

On FDA's Website

Guidance "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use"

http://www.fda.gov/npcguidance

Navigating FDA's Regulatory Programs



•NPC= New Protein Consulation as part of FDA's early food safety assessment program for new, non-pesticidal proteins

Final Consultation

- When a developer has assembled the information that it believes is adequate to ensure that the product is safe and lawful, the developer provides a summary of its safety and nutritional assessment to FDA.
- Basis: Authority in Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - (Section 409) New protein could be food additives, requiring FDA review and approval unless they are Generally Recognized as Safe
  - (Section Food labeling

Final Consultation (Who, How, What)

- You provide a summary of the safety and nutritional assessment typically includes the following types of data:
  - The name of the bioengineered food and the crop from which it is derived.
  - A description of the various applications or uses of the bioengineered food, including animal feed uses.
  - Characterization of the sources, identities, and functions of introduced genetic material.
    - Source should not be pathogenic or toxigenic, or an allergenic source

Final Consultation: Technical Effect/Expression Products

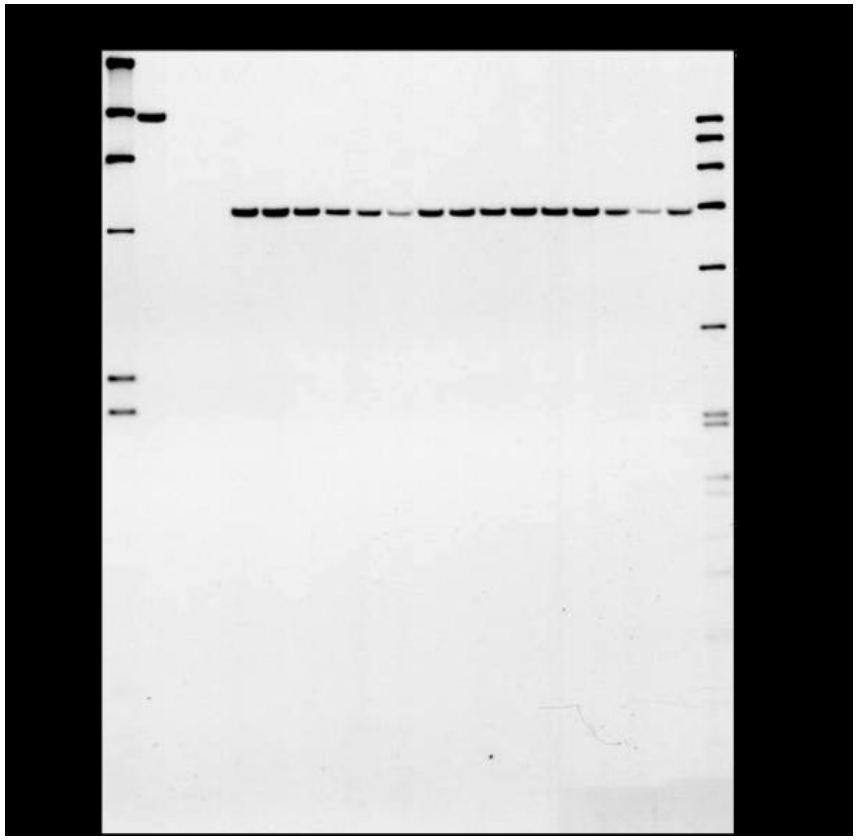
- Information on the purpose or intended technical effect of the modification, including any expected effect on the composition or characteristic properties of the food or feed.

- Information about the identity and function of any expression products encoded by the introduced genetic material, including an estimate of the concentration of any expression product in the bioengineered crop or food derived from it.
  - [Generally done by assessing levels in plant tissues used for food or feed]
  - Activity assays, Western Blots may be used

Final Consultation: Stability of New Trait

- Integrity of the insert across generations: Southern blot, PCR and sequencing

- Stable (phenotype) inheritance across generations: Chi-square analysis of the progeny



Final Consultation
The Protein

- Information addressing the safety of proteins or other new substances in the food. Information assessing the likelihood of allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed.
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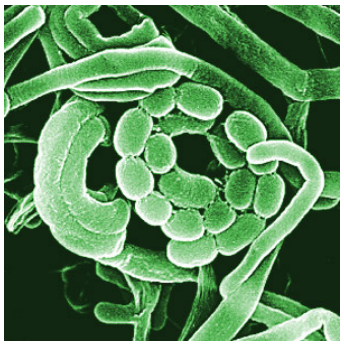
  - [May include in vivo/in vitro (feeding] studies of the protein] [Usually includes bioinformatic approach comparing sequence of new proteins to those of known protein toxins/allergens]
  - In vivo and In vitro testing



- Nature of the protein
- Function of the protein
- Toxicological studies, if needed

Final Consultation: Potential for Allergenicity



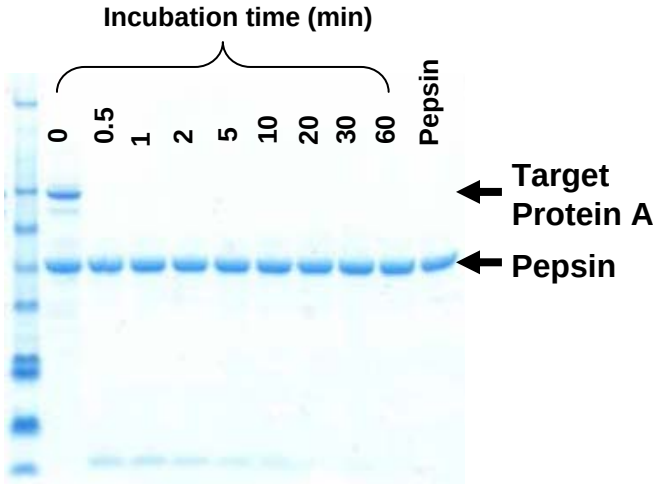





- **Bioinformatic analysis: Sequence similarity comparison of the new protein with that of known allergens (www.allergenonline.com)**
  - **> Identity of 35% or higher over 80 aa sliding window**
  - **> Identity of 8 or more contiguous aa sequence**
  - **Focus on likelihood for cross-reactivity with known allergens**

Final Consultation: Potential for Allergenicity

- **Digestibility in SGF (sometimes SGF and SIF) followed by SDS-PAGE and Coomassie blue or silver staining of the gel, as well as Western blot using specific antibodies to show the absence of detectable bands after incubation**
- **Sometimes serum testing (if appropriate)**



Final Consultation: Composition

- Composition
  - Compare the composition of the bioengineered food with that of food derived from the parental variety or related variety (when a parental variety is unavailable) or other commonly consumed varieties
  - Emphasize **important nutrients** and naturally occurring **toxicants or antinutrients** in the food.
- For allergenic crops: Address whether the genetic modification alters levels of known endogenous allergens
- Any additional information relevant to the safety and nutritional assessment of the bioengineered food

Final Consultation

- Case-by-case assessment – depends on the types of traits and nature of host plants, different types of data and information may suffice
  - For example, some plants are sources of allergens, toxicants
  - Some traits are based on new proteins, some on altered expression of existing proteins

On FDA's Website

Guidance "Guidance on Consultation Procedures Foods Derived From New Plant Varieties"

http://www.fda.gov/bioconprocguidance

Navigating FDA's Regulatory Programs

Final Consultation (continued)

- When all safety and regulatory issues have been resolved, the firm receives a letter indicating that the consultation is complete.

On FDA's Website

Response letter and memos of completed consultations are posted on FDA's Internet site at: http://www.fda.gov/bioconinventory

Final Consultations

- Codex Alimentarius Guideline for the Conduct of Food Safety Assessment of Foods Derived From Recombinant-DNA Plants CAC/GL 45-2003
- http://www.codexalimentarius.net/download/standards/10021/CXG_045e.pdf
- OECD consensus documents on compositional considerations for new varieties (available for selected crops)
- http://www.oecd.org/document/22/0,3746,en_2649_34385_46808854_1_1_1_1,00.html

Navigating FDA's Regulatory Programs

- Who can I contact to get started?

Robert Merker: robert.merker@fda.hhs.gov or premarkt@fda.hhs.gov