Truth in Food Labeling: It's Anyone's Guess

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Week 6

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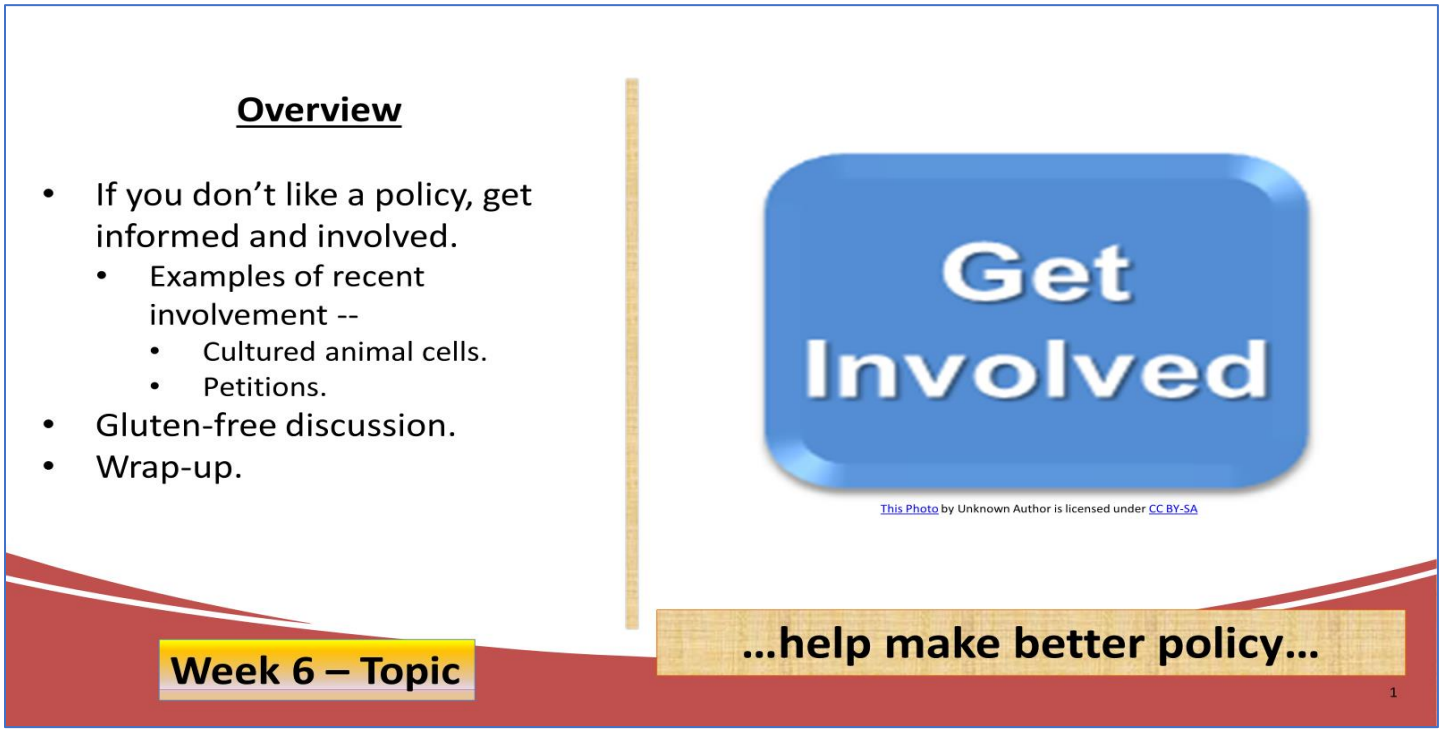

- Slide #1F – Week 6 – help make better policy…get involved…get informed…
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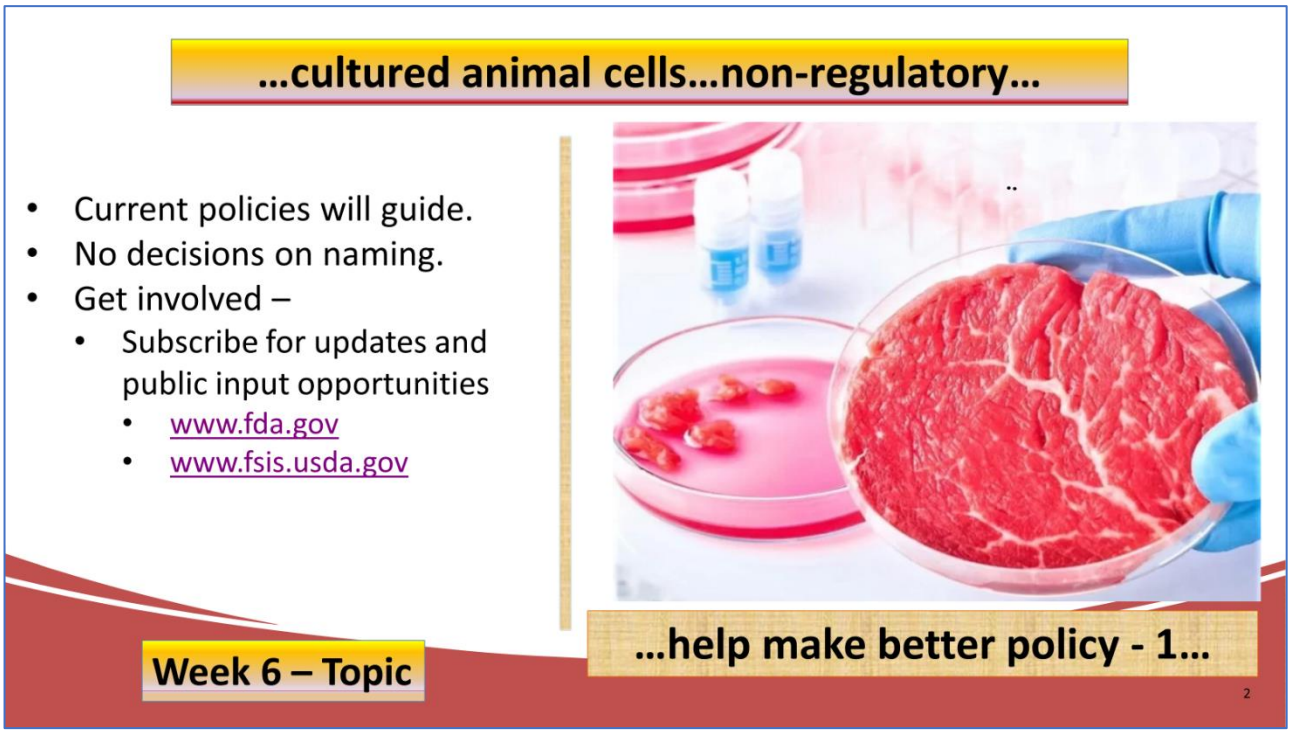
Slide #2F – help make better policy – 1…cultured animal cells for meat…non-regulatory approach…



- Slide #2F – help make better policy – 1…cultured animal cells for meat…non-regulatory approach…
  - Week 6 –
  - Major topic – help make better policy – 1 – cultured animal cells for meat – non-regulatory approach --
    - Pulled directly from the FDA website –
    - **"Human Food Made with Cultured Animal Cells –**
      - The ability to take a small number of cells from living animals and grow them in a controlled environment to create food is an emerging area of food science. Advancements in cell culture technology enable scientists to use animal cells obtained from livestock, poultry, or seafood to produce food products.
      - In 2019, FSIS and FDA established a formal agreement on how we would use our regulatory tools to help ensure that foods comprising or containing cultured animal cells entering the U.S. market are safe and properly labeled. This agreement laid out which parts of the process each agency would oversee and was the first step toward both developing the framework to support safe production of these foods and providing clarity to industry on the requirements for producing, distributing, and selling these foods in the U.S.
      - FSIS and FDA have held public meetings to better understand the science of animal cell culture technology, potential hazards, labeling considerations, and to listen to consumer concerns. FSIS and FDA will continue their open communication and engagement with stakeholders to foster innovation while ensuring the safety of our Nation's food supply.
    - **The Science of Making Foods with Cultured Animal Cells --**
      - There is a long history of scientific advances in biology, biochemistry, and engineering that have led to the innovations enabling the growth of animal cells outside of the animal itself, in a controlled environment, for food. The process, while complex, can be broadly summarized in a few steps.
        - **Step 1**: Scientists typically start with a sample of cells from the tissue of an animal or fish, a process that typically does not permanently harm or kill the animal. Some cells from the sample are selected, screened, and grown to make a "bank" of cells to store for later use.
        - **Step 2**: To make food, a small number of cells are taken from the cell bank and placed in a tightly controlled and monitored environment (e.g., a very large, sealed vessel) that supports growth and cellular multiplication by supplying appropriate nutrients and other factors.

- **Step 3**: After the cells have multiplied many times over into billions or trillions of cells, additional factors (e.g., protein growth factors, new surfaces for cell attachment, additional nutrients) are added to the controlled environment to enable the cells to differentiate into various cell types and assume characteristics of muscle, fat, or connective tissue cells.
- **Step 4**: Once the cells have differentiated into the desired type, the cellular material can be harvested from the controlled environment and prepared using conventional food processing and packaging methods.

- **Regulatory Oversight of Foods Comprised of or Containing Cultured Animal Cells –**
  - On March 7, 2019, FDA and FSIS agreed to establish a joint regulatory framework for human foods made from cultured cells of livestock and poultry to help ensure that any such products brought to market are safe, unadulterated, and truthfully labeled. Under this agreement, FDA will oversee the collection, growth, and the differentiation of living cells into various cell types, such as proteins and fats.. Regulatory jurisdiction transitions from FDA to FSIS during the harvesting stage of the cell-culturing process. FSIS will then also oversee the further processing, labeling, and packaging of these products.
  - Regulatory oversight of human foods comprised of or containing cultured animal cells depends on the animal species used as the original source of cultured cells, and it is based on the agencies' existing jurisdiction over products.
    - FDA is responsible for regulating all live animals to be used as food up until they are presented for slaughter.
    - For those animals intended for human consumption and regulated under the Federal Meat Inspection Act (FMIA) (i.e., cattle, sheep, swine, goats, and fish of the order Siluriformes) or the Poultry Products Inspection Act (PPIA) (i.e. chicken, turkeys, duck, geese, guineas, ratites, and squab), FSIS is responsible for regulation during slaughter, processing, packaging, and labeling.
    - For foods not regulated under FMIA or PPIA (e.g., all seafood other than Siluriformes fish and game meat) or foods intended for animal consumption, FDA has sole jurisdiction.. FDA has issued applicable requirements under both the Federal Food, Drug, and Cosmetic Act (FFDCA) and Public Health Service Act.
    - Therefore, food products made from the cells of species regulated by FSIS under FMIA and PPIA will be regulated by FDA during cell collection, selection, and growth and by FSIS during subsequent harvest, processing, and labeling. Food products for human consumption made from cells of species not subject to FSIS jurisdiction (e.g., seafood other than Siluriformes and game meat) and food products for animal consumption will be regulated solely by FDA.
  - View the USDA-FSIS and FDA pre-recorded webinar about the regulation of foods comprised of or containing cultured animal cells.
- **FDA REGULATORY OVERSIGHT --**
  - As described in the March 2019 formal agreement, FDA's approach to regulating products derived from cultured animal cells will involve a thorough pre-market consultation process and inspections of records and facilities. FDA will ensure that covered entities comply with applicable requirements, including facility registration and FDA's Current Good Manufacturing Practices and preventive control requirements.
  - FDA's pre-market consultation process evaluates the safety of foods made from cultured animal cells before they enter the market. As part of the pre-market consultation process, FDA evaluates the production process and produced biological material, including tissue collection, cell lines and cell banks, manufacturing controls, and all components and inputs. FDA encourages firms working on the culture of animal cells for food use to contact the agency early in the development phase to begin discussions. For human food, firms may contact the Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, at AnimalCellCultureFoods@fda.hhs.gov. If firms intend to market the cultured animal cell food products, or any of the byproducts generated during the production process, for animal food, the firm should contact the Center of Veterinary Medicine,

Division of Animal Feeds, at Animalfood-premarket@fda.hhs.gov. FDA believes that both the agency and individual firms will benefit from ongoing discussions as the firms make technical and strategic decisions.

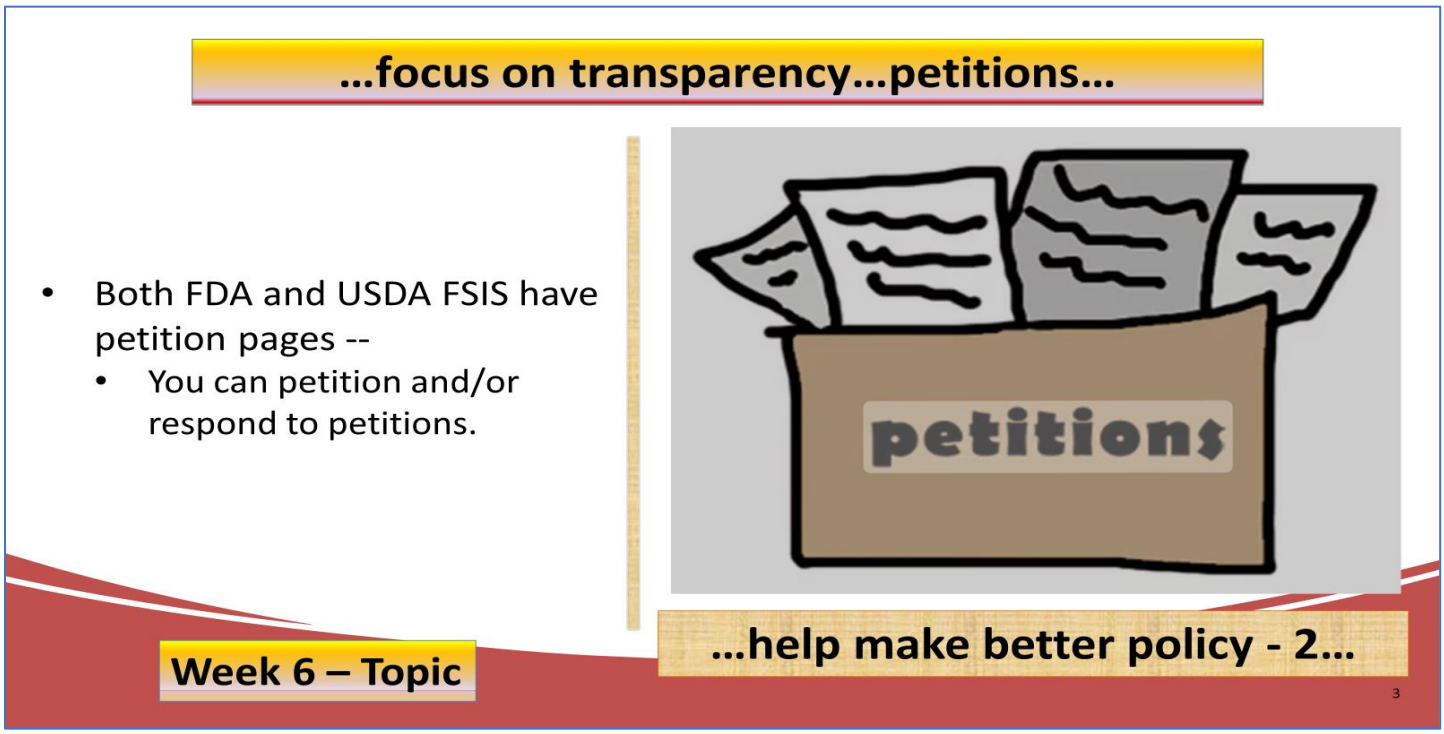
- After a successful pre-market safety consultation, FDA will conduct routine inspections on an ongoing basis, as well as other oversight activities at cell banks and facilities where cells are cultured, differentiated, and harvested. These inspections will help to ensure that potential risks are being managed and that biological material exiting the culture process is safe and not adulterated within the meaning of the FFDCA.
- In conducting inspections and other oversight activities, FDA will be able to draw on the results of the pre-market consultation and a thorough assessment of production records maintained by the facility. Should FDA inspections uncover areas of noncompliance, the agency will take appropriate action. FDA also will ensure that labeling of cell cultured products derived from animal species not subject to USDA jurisdiction is truthful and not misleading, consistent with coordinated FDA and FSIS principles for product labeling and claims.
- Learn more about the completed pre-market consultation and FDA's pre-market consultation process.

- **USDA REGULATORY OVERSIGHT –**
  - Establishments that intend to harvest or process cell-cultured meat and poultry must apply for and obtain a USDA grant of inspection for such products using existing procedures. Such establishments must meet all applicable FSIS regulatory requirements, including the requirements for ensuring sanitation and developing and implementing Hazard Analysis and Critical Control Points systems. The design of the facility must also meet USDA regulatory requirements. Establishments that harvest cell-cultured meat and poultry should complete an FDA pre-market safety consultation before applying for a USDA grant of inspection.
  - During the cell harvesting stage, i.e., when an establishment begins the process of removing cells from the sealed growth environment to be prepared for traditional food processing, FDA and FSIS will work together to coordinate the transfer of regulatory oversight to FSIS. FSIS will carry out inspections at establishments where cells derived from livestock and poultry are harvested or processed. FSIS inspectors will review batch records produced during cell culturing and verify compliance with applicable FSIS regulatory requirements during product processing, packaging, and labeling to verify the cell-cultured meat and poultry products are safe, wholesome, unadulterated, and truthfully labeled. If cell-cultured meat or poultry is shipped to other establishments for further processing into human food products, these establishments also will be subject to FSIS inspection.
  - FSIS inspection of cell harvest and processing will occur at a frequency of at least once per shift, the inspection frequency also required for processing traditional meat and poultry products. This level of verification is necessary for products to receive a USDA mark of inspection. Finally, FSIS will ensure that cell-cultured products are labeled truthfully and consistent with coordinated FDA and FSIS labeling principles. Under the requirements of FMIA and PPIA, all cell-cultured meat and poultry labeling must be preapproved by FSIS.
  - At this time, FSIS does not intend to establish new food safety inspection regulations governing cell-cultured meat or poultry, given its current regulations are immediately applicable to such products. However, as discussed in our advance notice of proposed rulemaking, FSIS does intend to publish new labeling regulations for such products.
- **Imports of FSIS-Regulated Meat and Poultry Products --**
  - Like imports of traditionally produced meat and poultry products, imports of meat and poultry products made from the cultured cells of livestock and poultry must originate from eligible countries and from establishments or plants certified to export to the United States. A country becomes eligible to export to the United States following an equivalence process, through which FSIS determines whether its inspection system achieves the same level of public health protection as is applied by FSIS in the United States. Additionally, the foreign food safety inspection system must provide standards equivalent to FSIS' system to ensure other non-food safety requirements

(such as accurate labeling and assurance that meat and poultry products are not economically adulterated) are met. At this time, FSIS has not deemed any country eligible to import cell-cultured meat or poultry products into the United States for sale for human food.
    - Imports of meat and poultry products made from the cultured cells of livestock and poultry will also be subject to all of the other FSIS requirements for imports, including labeling requirements and reinspection by FSIS at an official import establishment. These imports also will be subject to applicable requirements of USDA's Animal and Plant Health Inspection Services (APHIS) and the U.S. Customs and Border Protection (CBP).
- **Imports of FSIS-Regulated Meat and Poultry Products For Non-Commercial Purposes –**
    - As with traditionally produced meat or poultry products, 9 CFR 327.19, 381.207, and 590.960 allow small amounts of cell-cultured products to be imported into the U.S. without meeting FSIS requirements for specific non-commercial purposes, such as for personal use, display, laboratory examination, research, and evaluative testing. Our procedures on the import of such products are located in FSIS Directive 9500.8, Importation of Products for Other than Commercial Purposes. Once imported, such products are subject to the same procedures as those produced domestically (see FSIS Directive 7000.2, Experimental and Sample Products Policy).
    - The import of cell-cultured meat and poultry for non-commercial purposes also will be subject to applicable requirements of APHIS and CBP.
- **Imports of FDA-Regulated Products --**
    - Like all FDA-regulated foods, imports of foods comprising or containing cultured fish or seafood cells must meet the same legal requirements as domestically produced foods, including requirements related to the absence of unapproved food additives, color additives, or other substances that may adulterate the food.
    - Imported foods comprising or containing cultured fish or seafood cells must also meet specific agency requirements and are subject to oversight through multiple programs, including:
        - registration of any foreign facilities that engage in manufacturing, processing, packaging, or holding of the food,
        - prior notice to FDA that the food is being imported or offered for import, and
        - implementation of a foreign supplier verification program by the importer to ensure that their foreign supplier is producing food in a manner that provides the same level of public health protection as FDA's preventive controls regulations and to ensure that the supplier's food is not adulterated and is not misbranded with respect to allergen labeling.
    - Imported food products are subject to FDA inspection when offered for import at U.S. ports of entry. FDA may detain shipments of products offered for import that appear to be in violation of FDA requirements.
    - More information about FDA's requirements is available in these online resources:
        - Importing Food Products into the United States
        - Considerations for Determining Whether a Measure Provides the Same Level of Public Health Protection as the Corresponding Requirement in 21 CFR part 112 or the Preventive Controls Requirements in part 117 or 507: Guidance for Industry
        - What do importers need to know about the Foreign Supplier Verification Programs (FSVP) rule?
        - FDA Strategy for the Safety of Imported Foods
- **Announcements and Public Meetings --**
    - FDA and FSIS have held public meetings to better understand the science of animal cell culture technology, potential hazards, labeling considerations, and to listen to consumer concerns. FDA and FSIS will continue their open communication and engagement with stakeholders to foster innovation while ensuring the safety of our Nation's food supply.
    - **ANNOUNCEMENTS –**
        - USDA and FDA Launch Joint Webinar on Cultured Animal Cell Food and Feed Products (July 31, 2020)

- USDA and FDA Announce a Formal Agreement to Regulate Cell-Cultured Food Products from Cell Lines of Livestock and Poultry. (March 07, 2019)
- USDA and FDA announce joint public meeting on use of animal cell culture technology to develop products derived from livestock and poultry. (September 10, 2018)
- Statement from USDA Secretary Perdue and FDA Commissioner Gottlieb on the regulation of cell-cultured food products from cell lines of livestock and poultry. (November 16, 2018)

- **FDA AND FSIS PUBLIC MEETINGS –**
  - USDA and FDA Joint Public Meeting on the Use of Cell Culture Technology to Develop Products Derived from Livestock and Poultry. (October 23–24, 2018)
  - October 22, 2018: Science Board to the FDA Meeting Announcement. (October 22, 2018)
  - FDA Public Meeting on Foods Produced Using Animal Cell Culture Technology. (July 12, 2018)
  - Human Food Made with Cultured Animal Cells – https://www.fsis.usda.gov/inspection/compliance-guidance/labeling/labeling-policies/human-food-made-cultured-animal-cells#:~:text=FSIS%20inspectors%20will%20review%20batch,%2C%20unadulterated%2C%20and%20truthfully%20labeled.



- Slide #3F – help make better policy – 2…focus on transparency…petitions…
  - Week 6 –
  - Major topic – help make better policy – 2 -- focus on transparency – petitions --
    - At the U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS), there are numerous "truth in labeling" –
      - See https://www.fsis.usda.gov/policy/petitions.
      - Petitioner -- Environmental Working Group
        - Petition Number -- 23-04
        - Status – Receipt acknowledged
        - Submission Date – 4-27-2023
        - Petition Summary –
          - The petition requests that FSIS:
          - Prohibit the recently approved "Low-Carbon Beef" Claim.
          - Require third-party verification for similar carbon claims.
          - Require a numerical on-pack carbon disclosure when such claims are made
        - Available for online review or in Docket Room –
          - Copy of the full petition
          - USDA FSIS response acknowledgement letter
          - Copy of each comment submitted by the public (2 individual comment letters
      - Petitioner – Perdue Farms, LLC
        - Petition Number – 23-03
        - Submission Date – 3-16-2023
        - Petition Summary –
          - Conduct rulemaking to define separate "free range" and "pasture raised" claims for meat and poultry products.
          - Update guidance on claims related to living/raising conditions to ensure that the claims align with consumer expectations.
        - Available for online review or in Docket Room –
          - Copy of full petition

        - USDA FSIS response acknowledgement letter
        - Copy of each comment submitted by the public (15 individual comment letters)
    - What is a petition? –
        - A petition for rulemaking is a written request to issue, amend, or repeal a regulation administered by FSIS. A request to issue, amend, or repeal other FSIS policy documents, such as FSIS directives, notices, or industry guidelines, may also be submitted by petition. FSIS's regulations governing the petition process are in 9 CFR part 392. These regulations contain instructions on how to submit a petition to FSIS and describe the types of information that may help FSIS to review a petition in a more efficient manner. The regulations also permit interested parties to submit comments on a petition.
        - All petitions for rulemaking or policy changes submitted to FSIS are posted on the FSIS website. Comments submitted on petitions are also posted. When submitting an electronic comment on a petition, members of the public should identify the petition number in the subject line. Other than first and last name, FSIS does not post personally identifiable information (PII), such as personal addresses, phone numbers, or e-mail addresses on its website. Therefore, persons interested in submitting a comment on a petition are encouraged not to include PII with their comments. If a comment on a petition includes PII, the Agency will remove such information before posting the comment.
    - Once USDA FSIS or FDA considers the merits of the petition, either a letter of rejection is returned to the petitioner with an explanation as to why, or rulemaking and other policy options are initiated to possibly change the policy.
- For the Food and Drug Administration (FDA), there is no dedicated page to petitions.
    - However, FDA does maintain public access to all petitions received that are related to food labeling, such as food additives –
        - See – https://www.fda.gov/food/food-ingredients-packaging/food-additives-petitions.
- Subscribe to email alerts from both FDA and USDA FSIS on ways to participate in public meetings regarding food policy –
    - https://www.fda.gov,
    - https://www.fsis.usda.gov.

- Slide #4F – help make better policy…get involved…get informed – 3…fermented…gluten-free claims…
  - Major topic –
  - Get informed -2 -- focus on transparency – design of a regulation - fermented or hydrolyzed foods and gluten-free claim --
    - Twenty years ago, in 2004, the Food Allergen Labeling and Consumer Protection Act (FALCPA) was enacted to ensure, in part, that foods could be truthfully labeled as gluten-free.
    - Soon thereafter, in 2005, the Food and Drug Administration (FDA) held a public meeting on the issue to gather input from stakeholders about their concerns associated with the term gluten-free.
    - FALCPA did not specify how the FDA was to establish criteria for a gluten-free label claim other than the law said to provide for such a label, if feasible.
    - It was known at the time that there was a potential threshold level of gluten in a food below which it was unlikely that an individual with celiac disease would have an adverse health effect.
    - Through consensus of opinion among individuals with celiac disease, and the organizations that represented them, certain grains (i.e., wheat, rye, and barley) were identified as never being able to be classified as gluten free; no technology was available to reliable neutralize the harmful components of the gluten protein. There was no consumer consensus about excluding oats from being labeled as gluten-free.
    - Food manufacturers were interested in a government standard for gluten-free because a lack of its meaning created inconsistency, uncertainty, and liability.
    - Scientific experts, including medical professionals, identified that consumption of a daily dose of 500 ppm gluten definitively resulted in morphological damage to individuals with celiac disease. Consequently, considering daily consumption habits and serving sizes, a "safe harbor level" could be established at 20 ppm per serving and not exceed 500 ppm gluten for the day's consumption.
    - Through simulation modeling, individuals following a gluten-free daily diet (but consuming items labeled as gluten-free and containing no more than 20 ppm) likely would not reach a daily dose of 500 ppm. Further, at a level of gluten below 20 ppm, no adverse health impacts were identified in persons with celiac disease.
    - FDA could not base the gluten-free regulation on impact of individuals with gluten sensitivity (as opposed to being diagnosed with celiac disease) because there were no data available to quantitate medical costs.

Such individuals generally do not seek medical care due to there being a low likelihood of adverse health consequences other than gastro-intestinal distress and diarrhea.
    - Manufacturers identified that a more stringent threshold than 20 ppm would be too costly for compliance and that manufacturers would either not voluntarily make available gluten-free products or have a poor compliance rate.
    - Although science may evolve, 20 ppm currently is the lowest level at which analytical methods have been scientifically validated to reliably and consistently detect gluten across a range of food matrices.
    - Importantly, from the 2005 public meeting, it was identified that certain foods (i.e., those that are fermented or hydrolyzed) cannot reliable be analyzed quantifiably for gluten.
    - Rather than await scientific advancement for gluten detection methodology, FDA took initial steps to propose and then finalize a regulation to require that all foods that voluntarily bear a gluten-free label must not contain 20 ppm or more gluten. FDA made one exception or foods that were either fermented or hydrolyzed and that contained a gluten protein from either wheat, rye, or barley grain. The general regulation (21 CFR 101.91) covering all but fermented or hydrolyzed food went into effect in August 5, 2013, and is for the voluntary labeling of foods as gluten-free. FDA was unable to mandate gluten-free labeling for foods due to costs-benefit reasons in light of all gluten-containing grains already were required to be identified as allergens.
    - FDA mandated that food bearing a gluten-free claim must not exceed 20 ppm gluten in order that the label is truthful and not misleading; Note – although gluten may be present, the level of gluten is not known to cause harm and, thus, does not violate the adulteration statute; and further note – although gluten may be present, current technology cannot reliable determine quantifiable levels of gluten and is, thus, “absent” for legal purposes; if the science changes, this issue may be reassessed and adjusted.
- The following information was more specifically summarized from the regulatory impact analysis of costs and benefits, and from the proposed and final rulemakings.
    - High level summary of costs-benefits –
        - The cost-benefit analysis only considered the impact of the regulation on people with celiac disease and not others, such as individuals who do not have celiac disease but have gluten sensitivity.
        - The break- even point of the rulemaking, discounted at 7 %, for the percentage of individuals with celiac disease following a gluten-free diet realizing a health gain benefit from the regulation each year is –
            - 0.07 % based on harm done before and after implementation of the final regulation.
        - The annual cost range for the rulemaking was estimated at $7 - $11 M.
            - These costs accounted for testing ingredients for gluten, evaluating potential cross-contact, developing procedures to prevent cross-contact, relabeling product that likely won’t comply, and maintaining records.
        - The annual public health benefit range for the rulemaking was estimated at $8.8 - $9.1 M.
        - The effective date for the rulemaking was 30 days after publication in the Federal Register (i.e., the rulemaking published on August 13, 2020, and the effect date was October 13, 2020).
            - Note – the effective date means that neither FDA nor a consumer could not take enforcement action against a manufacturer for violation of the rulemaking provisions.
        - The compliance date for the rulemaking was August 13, 2021.
            - This date, one year after the effective date, was believed to provide sufficient time for all manufacturers to modify their production operations to come into full compliance with the regulation; in addition, this extensive period of time would have provided real cost savings to small entities.
            - This is the date that FDA will being enforcing the regulation.
            - Thus, there was a one-year period where unethical manufacturers could have marketed products as gluten-free and not likely face any ramifications unless deaths or other adverse consequences were identified and intentional fraud was likely to be proven by the FDA.

- This food labeling compliance date was six-months shorter than customarily provided for by the Uniform Compliance Date due to the public health impact of the rulemaking; normally, labeling regulations go into effect within a staggered 2-year period.

- Data gathering to support rulemaking –
  - In order to identify potential cost-benefit data, FDA collected samples of foods and analyzed them for the quantifiable levels of gluten.
    - FDA analyzed non-fermented and non-hydrolyzed foods and not fermented or hydrolyzed foods because the data for the fermented or hydrolyzed foods would have been unreliable.
    - FDA found a non-compliance level of 5 % for the non-fermented and non-hydrolyzed product.
    - FDA then surmised a conservative estimate of non-compliance for the fermented or hydrolyzed product at 1 %; note that other factors were used to obtain the 1 % estimate, including the degree of control procedures in place at establishments with prevention of cross-contact for allergens.
  - An estimate was needed on the number of individuals diagnosed with celiac disease that consumed foods daily and were at risk of harm due to a 500 ppm daily gluten intake from such food represented as gluten free.
    - Number of individuals with celiac was derived from a 2014 National Health and Nutrition Examination Survey (NHANES) that estimated 0.21 % of the US population had celiac disease.
    - Such individuals explicitly identified that they were told by a medical professional that they have celiac disease., amounting to 627,000 individuals older than 6 years.
    - Celiac individuals further identified their level of adherence to consuming products foods including those labeled as gluten free, including those foods that may contain fermented or hydrolyzed components. Thus, approximately 69 % claimed good adherence and 31 % claimed poor adherence. This then resulted in 432,000 people complying with a gluten-free diet and 194,000 for which the impact can be measured against. Using simulation modeling, health benefits could be assessed against 4,326 individuals.
    - FDA further assumed that a level of 20 ppm in any given food serving would eliminate any harm the could be associated with a daily value of 500 ppm.
    - QALY loss from baseline consumption and social cost — To estimate the benefits of being in good health, Quality-Adjusted Life Years (QALY) is used to measure the loss of well-being that an individual undergoes due to a disease condition. This includes estimates for medical expenditures caused by the illness. Attributes such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are assessed. Approximately 160 QALYs are lost annually from gluten-free food with levels of gluten of 20 ppm or higher. This then amounts to a social loss of $131.5 million to $79 million annually.
  - An estimate for the number of foods/manufacturers impacted was needed.
    - To generate this estimate, FDA contracted with the database owner of FoodEssentials/Label Insight, a private company that provides information on food label data to government, retailers, manufacturers, and app developers.
    - The database was searched in 2017 for hydrolyzed, fermented, or contain fermented or hydrolyzed ingredients, and that bear “gluten-free” or similar labeling.
    - Approximately 2,500 products identified, projected to be more likely at 5,000.
    - It was not known how many products were already labeled as gluten-free.
  - An estimate on the number of food manufacturing faculties that maintained written allergen control plans was conducted in a 2011 survey.
    - Approximately 45 % of all food production facilities had a written allergen control plan; therefore, about 75% of the 5,000 foods with gluten-free labeling claim already had a written plan for preventing the introduction of gluten into food product along with the control procedures for preventing cross-contact.

        - Through simulation modeling, written control procedures and testing (such as for grain, not gluten specifically) would most likely be incurred for about 1,250 products even though record availability would effect 5,000 products.
        - Testing cost dom $68 to $110 per sample, and most likely at $75; shipping samples to the laboratory would add cost, resulting in approximately $112 (overall, $620 annually per ingredient per facility and $1.5 to $3 M for all of industry).
    - An estimate for relabeling costs was conducted.
        - Assuming 5 % of industry did not comply with the 20 ppm limit, and relabeling cost was $7,000 per changed label, total industry cost for labeling would be $280,000 to $340,000.
    - An estimate for paperwork costs was needed for all facilities. Facilities are required to document their procedures and maintain them for review and copying for up to 2 years.
        - Costs estimated at $4.4 to $4.5 M.
- A more detailed review of the rulemaking follows, particularly the regulatory flexibility analysis of the costs and benefits –
    - Gluten-Free Labeling of Fermented or Hydrolyzed Foods -- (FDA Docket No. FDA-2014-N-1021).
    - Overview of the Cost/Benefit Impact Analysis for Federal agencies (including the U.S. Department of Agriculture, Food Safety and Inspection Service — USDA FSIS, and the Food and Drug Administration — FDA).
    - Selected Executive Orders require Federal Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. In doing so, Agencies must consider potential economic, environmental, and public health and safety benefits. To the extent permitted, a new proposed rule has to be offset by the elimination of existing costs associated with at least two prior regulations.
    - The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize significant impact on small entities. Small entities, by definition, generally have annualized costs that do not exceed one percent of their annual revenue. Consequently, the FDA certified that the gluten-free labeling of fermented products final rule would not have a significant economic impact on a substantial number of small entities. Had the the threshold been exceeded, FDA would have had to adjust the rulemaking to reduce costs (e.g., by delaying the implementation date).
    - The Unfunded Mandates Reform Act requires Agencies to conduct an assessment of anticipated costs and benefits possibly affecting State, local, and tribal governments, in the aggregate, or by the private sector. The threshold for consideration is set in the original law is set at $100,000,000 or more (adjusted annually for inflation) in any one year. Accounting for inflation, the current threshold is $156 million (based on the most complete figures from 2019). The FDA certified that the gluten-free labeling of fermented products final rule would not meet this threshold. Had the threshold been exceeded, the FDA would have had to adjust the rulemaking to reduce costs (e.g., by delaying the implementation date).
    - Summary from the final rule's executive summary — Requirements are established for gluten-free labeling for foods that are fermented or hydrolyzed or that contain fermented or hydrolyzed ingredients (e.g., cheese, yogurt, vinegar, sauerkraut, pickles, green olives, beers, and wine, or hydrolyzed plant proteins used to improve flavor or texture in processed foods such as soups, sauces, and seasonings). Note that most of these aforementioned products do not contain gluten protein. However, manufacturing processes may add a gluten containing ingredient but in so doing, the fermentation or hydrolyzation process may mask the presence of gluten. These requirements are needed to help ensure that people with celiac disease are not misled and receive truthful information regarding products labeled as gluten-free. Importantly, the FDA is not aware of any scientifically valid method effective in detecting and quantifying with precision the gluten protein content of fermented or hydrolyzed foods in terms of equivalent amounts of intact gluten proteins. Consequently, the FDA plans to evaluate compliance based on records that are made and kept by the manufacturer and made available to the FDA for review and copying. The records must demonstrate that for foods labeled as gluten-free, the food or ingredients must be "gluten-free" before fermentation or

hydrolysis. Manufacturers must also evaluate the potential for gluten cross-contact and, if identified, have implemented measures to prevent introduction of gluten into the food during the manufacturing process. The gluten-free fermented or hydrolyzed food must comply with the requirements of the 2013 final rule on gluten-free food labeling (e.g., contain less than 20 parts per million — ppm intact gluten). The product must be validated extensively for the detection of gluten in both raw and cooked or baked products. In determining the 20 ppm limit, the FDA considered multiple factors including currently available analytical methods and the needs of people with celiac disease, as well as factors such as ease of compliance and enforcement, and stakeholder concerns, economics, trade issues, and legal authorities.

- "Gluten-free" is defined to mean — A food that does not contain an ingredient that is a gluten-containing grain; an ingredient that is derived from a gluten-containing grain and that has not been processed to remove gluten; an ingredient that is derived from a gluten-containing grain and that has been processed to remove gluten if the use of that ingredient results in presence of 20 ppm or more gluten in the food; or inherently, does not contain gluten, and that any unavoidable presence of gluten in the food is below 20 ppm gluten.
- A food that bears the claim "no gluten," "free of gluten," or "without gluten" in its labeling and fails to meet the requirements for the "gluten-free" claim will be deemed to be misbranded.
- Manufacturers of "gluten-free" foods must retain records for at least two years after introduction or delivery for introduction of the food into interstate commerce. FYI, the two-year period takes into account that most foods, including those that are frozen or preserved by canning, will be consumed within this period of time.
- A hydrolyzed food is defined in 21 CFR, Chapter 1, Subchapter B, Part 102, Subpart B, Section 102.22. For a protein hydrolysate (defined within Subpart B — Requirements for Specific Nonstandardized Foods -- Section 102.22 – Protein hydrolysates), the common or usual name must be specified to the ingredient and must include the identity of the food source from which the protein was derived. "Hydrolyzed wheat gluten," "hydrolyzed soy protein," and "autolyzed yeast extract" are examples of acceptable names. "Hydrolyzed casein" is also an example of an acceptable name, whereas "hydrolyzed milk protein" is not an acceptable name for this ingredient because it is not specific to the ingredient (hydrolysates can be prepared from other milk proteins). The names "hydrolyzed vegetable protein" and "hydrolyzed protein" are not acceptable because they do not identify the food source of the protein.
- Costs and benefits — Full compliance with this final rule would have annualized costs of about $7 million to $11 million per year at a 7 % discount rate. For the final rule to break-even with costs, the annualized benefits would need to be at least $9.1 million at a 7 % discount rate. Based on the FDA simulation analysis, the final rule would break-even with primary cost estimates discounted at 7 % if at least 0.07 % of estimated individuals with celiac disease following a gluten-free diet benefit from the rule each year.
- From a summary of the Final Regulatory Impact Analysis, a number of Executive Orders require Federal Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, and public health and safety). and equity. In addition, to the extent permitted by law, any proposed rule is to be offset by the elimination of existing costs associated with at least two prior regulations. The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small entities, by definition, may have annualized costs that do not exceed one percent of their annual revenue, the government agency proposing the regulatory action must certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act requires an assessment of anticipated costs and benefits before issuing the rule. The assessment includes any Federal mandates that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year. The most current assessment from 2019 is

$156 million. This rule does not exceed this threshold. [This paragraph is general and not specific] Summary of Costs and Benefits — The final rule (now a regulation enforceable by law) requires that, for foods that are fermented or hydrolyzed or contain one or more fermented or hydrolyzed ingredients, and bear any of these claims "gluten-free," "no gluten," "free of gluten," or "without gluten," the manufacturer must have records that demonstrate adequate assurance that the food, or fermented or hydrolyzed ingredient(s), is "gluten-free in compliance with 21 CFR 101.9(a)(3). In addition, the final rule requires documentation by the manufacturer that any potential for gluten cross-contact has been adequately assessed, and where such potential has been identified, that the manufacturer has implemented measures to prevent the introduction of gluten during the manufacturing process. The final rule also provides that FDA will evaluate compliance of distilled foods, such as distilled vinegar, by verifying the absence of protein using scientifically valid analytical methods that can reliably detect the presence of protein or protein fragments in the food

- Need for the rulemaking — Celiac disease is a hereditary, chronic inflammatory disorder of the small intestine triggered by the ingestion of gluten, which occurs in barley, rye, wheat, and crossbreeds of these grains. The main protein of barley is secalin, of rye is hordein, and of wheat gluten is gliadin. These proteins are components of gluten that create an immunopathogenic element of concern and are active in celiac disease, causing harm to people with this disease.
- In the Federal Register (FR) on August 3, 2013 (78 FR 47154), the FDA published a final rule for the voluntary use of term "gluten free." The FDA was not able to justify, through cost-benefit analysis the mandatory labeling of foods with gluten, such as for allergens. Further, he 2013 final rule did not require manufacturers to tests foods for the presence of gluten. However, manufacturers could choose to do so to ensure that the food does not contain 20 ppm or more gluten. The FDA could choose to analyze foods for the presence of gluten using a scientifically valid method that can reliably detect the presence of 20 ppm gluten in a variety of food matrices, including both raw and cooked or baked products. Through comments received in response to the proposed rule for gluten-free labeling of foods (72 FR 2795, January 23, 2007), the FDA became aware that fermented or hydrolyzed foods cannot be tested for a quantitative measure of intact gluten using currently available analytical methods. A scientifically valid method is one that is accurate, precise, and specific for its intended purpose and where the results of the method evaluation are published in the peer-reviewed scientific literature. Current methodology for detecting gluten rely upon quantifying total gluten contents; fermentation and hydrolysis cause fragmentation of gluten and it is those fragments that cannot be reliable detected and quantified at this time.
- Legal authority — The Food, Drug, and Cosmetic Act (FDC&A) directs the Secretary of Health and Human Services, in consultation with appropriate experts and stakeholders, to "issue a rule to define, and permit use of, the term "gluten-free" on the labeling of foods. Foods shall be deemed to be misbranded if its labeling is false or misleading in any particular. Food labeling is misleading if it fails to reveal facts that are material with respect to the consequences, which may result from the use of the food to which the labeling relates under conditions of use as are customary or usual. The Act also provides authority to requires records be maintained by manufacturers to demonstrate the truthfulness of the label in absence of a valid scientific methodology, and that the FDA is authorized to review and copy the records as part of its responsibility to ensure the truthfulness of the label claim. Failure to make and keep, and provide the records to the FDA, would result in the food being misbranded.
- Comments on the proposed rule — Over 500 comments were received by the FDA. The comments were submitted by consumers and consumer groups, trade organizations, industry, public health organizations, public advocacy groups, and other organizations. Similar comments were grouped together and responses were provided for each.
- Overall, comments focused on the truthfulness of the gluten-free labeling claim.
    - Commenters asked for exemptions from gluten-free labeling testing and/or documentation requirements. However, the final rule does not make any exemptions. All foods may, at some point during manufacturing, have a risk of cross-contact with a gluten-containing grain

depending on manufacturer operations, sources of ingredients, movements through the supply chain, and distribution. Further, no exception was made regarding defining the term "fermented food" as only a food or ingredient derived from a gluten-containing grain by fermentation due to the possibility of cross-contact. In addition, regarding commercially grown enzymes produced by microbes grown on media containing wheat, no exemption was provided; again due to the possibility of cross-contact. Even for distilled products in which the process of distillation is known to remove all protein, the potential for cross-contact is still valid due to poor manufacturing practices; thus, no exception was made for distilled products.

- Concern was raised about the labeling of gluten-free beer in which the Treasury Department's Alcohol and Tobacco Tax and Trade Bureau (ATTTB) is responsible for labeling of malt beverages under the Federal Alcohol Administration Act (FAAA). Certain other beers are subject to the FDA labeling regulations. Regardless, the gluten-free labeling must still be truthful and not misleading in accordance with the FDA authorizing statutes (e.g., the Federal Food, Drug, and Cosmetic Act— FFDC&A), for which enforcement discretion will be exercised. On February 11, 2014, the Alcohol and Tobacco Tax and Trade Bureau (ATTTB) issued an interim policy on gluten content statements in the labeling and advertising of beverages or beers it regulates. The interim policy allows the use of the following qualifying statement to inform consumers: "Product fermented from grains containing gluten and [processed or treated or crafted] to remove gluten. The gluten content of this product cannot be verified, and this product may contain gluten." Or "This product was distilled from grains containing gluten, which removed some or all of the gluten. The gluten content of this product cannot be verified, and this product may contain gluten." Regardless, beers under the jurisdiction of the FDA that are made from gluten-containing grains cannot bear a gluten-free claim without documentation to support the truthfulness of the claim.

- Effective and compliance dates —The final rule became effective 30 days after issuing in the Federal Register. Recognizing that manufacturers of applicable product will need time to review their production processes to ensure that their products comply with the final rule requirements. Consequently, the compliance date of this final rule was set for one year after issuing in the Federal Register. The compliance date for this food labeling final rule is actually six-months earlier than expected (i.e., before the end of the two-year Uniform Compliance Date period) due, in part, to a concern for public health.
- Economic analysis of impacts —
- The cost estimates of this final rule range from $7 million to $11 million. The costs are associated with testing ingredients for gluten, evaluating potential for cross-contact, developing and carrying out written standard operating procedures for preventing gluten cross-contact, relabeling products that cannot be brought into compliance, and maintaining records of these activities.
- The benefits of this final rule range from $8.8 million for $9.1 million. The benefits are associated with health gains for people with celiac disease using gluten-free labeled foods while maintaining a gluten-free diet. Estimates are based on harm done by dietary gluten intake from a gluten-free diet before and after the rule. In addition, the break-even point requires at least 0.07 % of estimated individuals with celiac disease following a gluten-free diet.
- Federalism — The Food and Drug Administration made clear that this final rule is intended to preempt any State and local laws or regulations that are not consistent with the Federal requirements. This preemption is to best ensure that consumers are not confused or misled about gluten-free labeling.
- No public comments were received on the preliminary economic analysis. Inputs for the simulated benefits analysis and costs model were updated with more recent data. The analysis now uses wage population, and quality-adjusted-life-year (QALY) data from 2018. [One QALY is equal to 1 year of life in perfect health; QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale).]. The final analysis incorporates updated peer-reviewed estimates of celiac disease prevalence

and accounts for potential changes in baseline consumption of covered products following publication of the broader 2013 gluten-free final rule. Average values were used in calculations. Before the FDA issued the 2013 broader gluten-free final rule, approximately 5 % of foods labeled "gluten-free" contained more than 20 ppm of gluten. An estimate of 1 % of fermented and hydrolyzed foods contain more than 20 ppm of gluten. Thus, approximately 4,326 individuals diagnosed with celiac disease consumed such foods daily and were at risk of harm due to a 500 ppm daily gluten intake from such food represented to be "gluten free." "Harm" to people with celiac disease reflected the morphological damage that 500 ppm of gluten per day was shown to cause to those with celiac disease. The 20 ppm limit of the final rule would eliminate this harm.

- To estimate of the number of manufacturers affected by the final rule, the FoodEssentials/Label Insight database [a private company that provides information on food label data to government, retailers, manufacturers, and app developers] was searched in November 2017 for foods that are hydrolyzed, fermented, or contain fermented or hydrolyzed ingredients, and bear the "gluten-free" or similar labeling. Approximately 2,500 products were identified. Based on experience with the market and the database, the more realistic number of products impacted was changed to 5,000. Since there is no database to identify how many products are produced in each facility, it was assumed that each product and its production line would be tested separately and would require a separate evaluation of the standard operating procedures. Similarly, it was not known how many affected products were already labeled as gluten-free. A 2011 survey of food industry practices showed that about 45 % of all food production facilities had a written allergen control plan, and about 39 % required certificates of analysis for ingredients. Given that manufacturers of food labeled as gluten-free likely were marketing to customers who care more about gluten cross-contact, it was estimated that about 75 % of the 5,000 foods with a gluten-free labeling claim already had a written plan for preventing the introduction of gluten into the food product that includes the testing of ingredients and also procedures for evaluating and preventing gluten cross-contact. Therefore, it was estimated for the simulation analysis that testing and standard operating procedures would be be incurred for about 1,250 products. Still, costs for making records available to the FDA, including for allergen control, would affect 5,000 products.
- For testing costs, gluten testing can be done by sending ingredient samples to a testing company and by using test kits on site. Testing companies charge between $68 and $110 per sample, with a best estimate of approximately $75. With shipping costs included, the total estimated cost for testing was $112. Overall, the testing costs were estimated to be $620 per year per ingredient. For all of industry, the testing costs were estimated to be $1.5 million to $3 million.
- For measures to prevent cross-contact — The total estimated cost of developing standard operating procedures was $1.6 million to $1.7 million.
- For relabeling costs — As a consequence of the final rule, some manufacturers may have to change current labels to comply with an added gluten-free label whereas others may decide to no longer use a current gluten-free label because of an inability to comply with the final rule. It was estimated that 5 % of products would not comply with the 20 ppm limit and would thus have to make a change in labeling. Using well-established procedures to estimate labeling cost changes, the midpoint of average estimated cost, adjusting for inflation, was approximately $7,000 per changed label. Consequently, the total cost industrywide was estimated to range between $280,000 and $340,000.
- Paperwork costs — The total estimated cost for maintaining appropriate records, particularly of preventive measures for cross-contact, was $4.4 million to $4.5 million.
- Benefit estimates — The harm done by dietary gluten intake from a gluten-free diet before and after the final rule was simulated. The simulation addressed the number of people harmed under the baseline (full compliance with the existing gluten-free rule from 2013 for other products) and the amount by which they were harmed, and then assess for the break-even point.
- Number of individuals with celiac disease on a gluten-free diet — From a 2014 National Health and Nutrition Examination Survey of non-institutionalized civilian population in the U.S., 0.21% of the population have been told they have celiac disease by a medical professional. With a U.S. population

of 289.6 million in 2018, this amounts to 627,000 individuals older than 6 years. Studies involving interviews by nutritionists with caretakers for children and adults concluded that approximately 82 % of celiac patients had good adherence to a gluten-free diet and knowingly ate gluten up to once monthly. Consequently, there are 432,600 people complying with a gluten-free diet and 194,400 for which the impact of the rule can be measured against. An estimate was made of the percentage of products labeled gluten-free but that contained gluten at or above 20 ppm. Since there was no accurate measure of gluten content in fermented or hydrolyzed product, a similar ratio was used. Serving sizes of foods consumed were estimated using National Health and Nutrition Examination Survey results. Simulation modeling then estimated that 4,326 individuals with celiac disease were harmed by the consumption of fermented or hydrolyzed foods labeled as gluten-free and containing 20 ppm or more gluten as part of their diet. The highest amount of gluten that can be consumed daily without causing harm is unknown and likely varies from person to person. For purposes of this analysis, a value of 50 ppm of gluten per day was used because this amount has been shown to cause morphological damage to most individuals with celiac disease in a double-blinded study. Thus, the simulation results in 1.6 % (1,600) of the simulated diets containing more than 50 mg (Note — 50 mg is the same as 500 ppm) of gluten.

- QALY loss from baseline consumption and social cost — To estimate the benefits of being in good health, Quality-Adjusted Life Years (QALY) is used to measure the loss of well-being that an individual undergoes due to a disease condition. Medical expenditures caused by the illness. Attributes such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are assessed. Approximately 160 QALYs are lost annually from gluten-free food with levels of gluten of 20 ppm or higher. This then amounts to a social loss of $131.5 million to $79 million annually.
- Gluten consumption with the final rule in effect — Consumer purchasing habits likely would change if some foods no longer are available because they no longer bear a gluten-free label. Lost pleasure from substitution of foods was considered in the cost-benefit for the rule.
- Alternative consideration — Considered not allowing the gluten-free claim on fermented or hydrolyzed foods as an option. Number of entities impacted — At least 97 % of approximately 16,000 businesses were small in size in terms of revenue or number of employees. Since applying the label is voluntary, the impact is significantly reduced for these entities.
- Compliance follow-up to the original “broader” final rule — In 2017, the FDA released a report on the compliance with the regulation. Of 702 samples from more than 250 products labeled as gluten-free, only one of the products did not comply with the 20 ppm limit. That product was recalled and subsequent testing did not find any product that violated the regulation.

Slide #5F – take a stretch...

- Slide #5F – take a stretch...
  - Major topic –
  - 10-minute break.

Slide #6F – keep looking for answers-- wrap up...

- Slide #6F – keep looking for answers -- wrap up...
  - Major topic –
  - Final discussion with question and answers.

Copy of each week's Slide #1 and slide color name…

Week 1 – Office 2013

Week 2 – Red Violet

Week 3 – Marquee

Week 4 – Violet II

Week 5 – Violet

Week 6 – Office 2007