Overview and Summary of NABC 26
New DNA-Editing Approaches: Methods, Applications and Policy for Agriculture

Allan Eaglesham[1] and Ralph W.F. Hardy
North American Agricultural Biotechnology Council (NABC)
Ithaca, New York

aeaglesh@twcny.rr.com

OVERVIEW

Recently developed technologies—zinc finger nucleases (ZFNs), meganucleases (MNs), transcription activator-like effector nucleases (TALENs) and CRISPRs (clustered regularly interspaced short palindromic repeats)/Cas9—offer highly efficient and accurate means of DNA/gene editing that are being rapidly adopted by researchers. These technologies—the focus of the twenty-sixth annual conference of the North American Agricultural Biotechnology Council (NABC 26)—promise to greatly speed progress toward introduction of crop and livestock genotypes with valuable new traits not achievable in reasonable timeframes using conventional breeding techniques. Importantly, these technologies, responsible for creation both of targeted gene deletions and improved replacement genes, can be eliminated by conventional breeding to yield plants and livestock that potentially will not be classified as genetically engineered/modified organisms (GMOs).

The presentations at NABC 26 were grouped in six areas:

- Keynote addresses,
- Technology descriptions,
- Uses of the technologies,
- Non-governmental regulatory aspects,
- Governmental regulatory aspects, and
- *Student Voice*.

[1]We are grateful to Don Weeks (University of Nebraska-Lincoln) for his suggestions for improvement in this chapter.

As editors, we have selected—based on our judgment—significant statements made by speakers in the keynote and plenary sessions, as well as in the Q&A and the "tie-up" sessions and the *Student Voice* report. As such, this overview includes inputs from many of the attendees.

Since regulations in the United States, Canada, and Europe differ substantially, we have grouped statements on regulatory aspects accordingly; also, we include a global grouping with broad relevance. This volume—*NABC Report 26*—provides full reports for the interested reader. The quality and quantity of these articles are excellent and cutting-edge, underpinning the development of new tools and their applications for plant and animal agriculture and for appropriate science-based risk/benefit oversight to ensure safety for food, feed and the environment.

Although the nominal focus of the conference was on DNA editing, the dialogue frequently turned to genetically engineered plants and animals (GMOs). The discussions touched upon in this chapter are presented under these two headings, in broad categories, with the objective of providing a relatively brief overview of the conference proceedings:

- **DNA Editing of Plants and Animals**
  - — Technology
  - — Uses
  - — Regulatory Issues
  - — General Considerations
- **Genetically Engineered (GM) Plants and Animals**
  - — Uses
  - — Regulatory Issues
  - — Labeling
  - — General Considerations.

SUMMARY

DNA Editing of Plants and Animals

Technology

- Zinc finger nucleases (ZFNs) were the first widely used gene-editing tools.
- ZFNs were made up of two separate zinc fingers (designed to bind specifically to two separate, but closely spaced, DNA sequences) with each ZF carrying a nonspecific nuclease domain that was designed to dimerize and cut the DNA sequence between the two zinc fingers.
- The next major step was the demonstration of ZFN activity in whole cells and organisms— where DNA cleavage by ZFNs (or other nucleases) can lead to gene knockout or gene replacement.
- Additional work showed efficacy in cultured human cells, in plants and in nematodes. ZFNs and other nucleases have now been used successfully to modify the genomes of more than fifty distinct organisms.

- A drawback to the use of ZFNs was the difficulty of deriving reliable designs for new targets.
- The discovery of a simpler DNA-recognition code in transcription activator-like effectors (TALEs) in *Xanthomonas* bacteria led to a new platform for targeted cleavage.
  - TALENs were rapidly adopted in preference to ZFNs, particularly in research labs, for the simplicity of their design, for the higher rate of success of new designs, and for the apparent sequence specificity of the ultimate reagents.
- The latest additions to the tool kit are the CRISPR/Cas RNA-guided nucleases. In this case, recognition is mediated by a guide RNA.
  - In addition, only a single protein, Cas9, is required for DNA cleavage. It doesn't need to be modified when the target is changed; only the guide RNA needs to be changed. These features have led to rapid adoption of CRISPR nucleases.
- Repetitive patterns in the genome of *Escherichia coli*, discovered over 25 years ago, have been found to be a defense system against viruses. Modification of this natural defense mechanism led to the development of the CRISPR/Cas9 system now used for gene editing.
- Ultimately, these targetable nucleases make breaks only at the desired DNA targets. Everything that happens afterward depends on cellular DNA-repair activities. This means that the outcomes of nuclease-mediated targeting events may be somewhat different, but usually result in desired gene knockouts or gene-replacement events.
- The majority of repairs proceed by a process called non-homologous end-joining (NHEJ) DNA repair—an error-prone process that often results in loss of gene activity (*i.e.* gene knockout).
- If extra copies of a modified gene are present at the time of DNA cleavage, homologous recombination (HR) can take place at the cut site. This results in the highly accurate installation of a new gene with new and potentially favorable activity.
- Genome engineering, as typically practiced, uses sequence-specific nucleases that recognize unique sites in the plant or animal genome and introduces targeted DNA double-strand breaks (DSBs).
- There are four classes of sequence-specific nucleases: Transcription activator-like (TAL) effector nucleases, zinc-finger nucleases, homing endonucleases or mega-nucleases and CRISPR/Cas9.
- Because no protein engineering is required and targeting is achieved simply through base pairing, CRISPR/Cas9 has emerged as the reagent of choice for making targeted chromosome breaks.

- The most striking feature of TAL effectors is the central repeats that are mainly 34 amino acids in length. The repeats are nearly identical except for the two amino acids at positions 12 and 13, the so-called variable di-amino acids. The di-amino acids actually determine the specificity of DNA binding for each repeat.
- Importantly, after TALENs have been introduced into plants and cause the desired genetic changes, the DNA sequences that contain the transgenic TALEN genes and the associated selectable-marker genes can be segregated out in progeny through standard genetic crossing. This results in plants that contain only the desired mutations and valuable new agronomic traits, but not the transgenes.
- The CRISPR/Cas9 system, is more affordable, remarkably easier to use, and well-suited for multiplex gene targeting and high-throughput genome-wide gene editing at similar or even higher efficiencies than ZFNs and TALENs.
- For many species, delivering the gene-editing tool into the cell remains a challenge.
- We have multiple competing platforms. If it is too expensive to use a TALEN to modify a crop, then a CRISPR approach may be a valid alternative.
- Synthetic biology is seen as an important new means of constructing modified organisms to produce products of value, with TALENs and CRISPERs as enabling tools.
- One prospect that scientists are currently excited about is applying Cas9 towards *in vivo* somatic cell editing.
- We are continuing to better understand the subtle properties of TAL effectors in part by studying them in their native context, but we are far from having fully exploited them in DNA-targeting applications.
- The promise of non-transgenic breeding technologies is their extraordinary breadth.
- EXZACT™ Precision Technology is based on ZFNs and has been used commercially to successfully modify field crops that soon will be in the marketplace.
- Using ZFNs, it is possible to target multiple genes to the same location, which decreases the number of loci involved in breeding and facilitates multi-trait product development.
- EXZACT™ Precision Technology is available and accessible both to the public and private sectors through a Dow AgroSciences' licensing agreement.
- Targeted gene deletion, gene editing and gene replacement have been demonstrated in tobacco, maize, canola, tomato and wheat.
- Enzymes and transcription factors from different organisms have different efficiencies. HR technologies allow for production of closely related enzymes and transcription factors, differing by one or two amino acids at the active site to be precisely modified, effectively mutagenizing a low-efficiency enzyme or transcription factor for greater efficiency.

— We can go in and make pretty much any modification we want in any gene we want whether it encodes an enzyme, a structural protein or a transcription factor. That capacity is currently there. As we look towards the future, designing for desired variations *in vivo* is certainly a possibility.

- Anyone setting out to achieve genetic modification with these gene-editing technologies must start with "a" genome of "a" plant for which the sequence is already known.
- In regard to regulatory oversight, one reason for needing a definition of gene editing is to "anchor" regulation and policy decisions. If you break or lose a DNA sequence—both forms of gene editing—regulatory guidance from the USDA says that this is not a regulated article. But nucleotide addition or replacement is more tricky. How many nucleotides over what span of DNA constitute an edit versus creation of a transgene?
  — Some scientist are uncomfortable saying what number of nucleotides for what span of DNA it would be, but perhaps such a definition will be needed.

Uses

- Whereas multiple strategies must be deployed to achieve food security, it is clear that amongst these is the need to accelerate the rate of crop improvement. Recent advances in genome engineering promise to make this possible. From targeted mutagenesis to targeted gene insertion, genome editing is transforming plant science, making it possible to create genetic diversity with precision, efficiency and control.
- Targeted mutagenesis is particularly valuable for altering gene activity or function.
  — Removing toxins, such as ricin from castor oil, or anti-nutritionals, such as trypsin inhibitors from soybean, are potential traits of value. Similarly, antigenic determinants that cause allergic reactions could be removed from nut or grain proteins.
- The real advantage of mutagenesis with sequence-specific nucleases is their precision. Traditional methods of mutagenesis that use chemicals, X- or gamma-rays, transposons or T-DNA provide virtually no control over where in the genome mutations are created.
- Sequence-specific nucleases rarely cleave at unintended or off-target sites and, thus, typically create mutations only at the intended sites.
- The high level of control afforded by DNA repair through HR makes it possible to create plant varieties with complex traits, such as tolerance of biotic or abiotic stress or that more efficiently use inputs such as fertilizer and water.
- With gene targeting, late-blight resistance in potato can be achieved in a much shorter timeframe than with traditional breeding and with only subtle alterations to the genome.
- The promise of gene editing in livestock is enormous.

- Gene editing—which allows geneticists to introduce (introgress) any natural trait into any breed without the use of recombinant DNA—has the potential of improving animal genetics for meeting increasing agricultural and biomedical needs with minimal environmental impact.
- With precision inactivation (knockout, KO) of specific genes required for organ development *in utero*, pigs could be used as bioreactors for production of donor-specific organs/tissues by *blastocyst complementation* or *exogenic organ production*.
- Gene editing saves about eight generations of backcrossing and the entire attendant screening for alleles desirable to industry.
- Gene editing is not limited to single changes. Because of the high efficiency of the procedure, multiple selected mutations can be simultaneously introduced into genomes.
- If a genetic alteration is not detrimental to an animal, it is highly unlikely it would be to humans.
- An important goal in developing TALEN technology for rice is to apply it for our basic scientific research and for breeding disease-resistant rice varieties.
- Collectively mutating all three disease-susceptibility-gene (S-gene) promoters causes plants to become durably and broadly resistant to bacterial blight disease.
- We have been using TALEN technology also to generate genetic materials of rice to gain basic understanding of the roles of rice SWEET (sucrose-transporter) genes in plant growth, development and production in addition to disease susceptibility.
- TALENs were successfully applied to edit the promoters of two disease-susceptibility SWEET genes to render the otherwise susceptible rice resistant to a broad range of bacterial-blight pathogen field isolates.
- CRISPR/Cas9 is highly efficient for genome editing in rice.
- In the United States, Cibus' commercial herbicide-resistance canola (***SU Canola***) is now in the launch phase. In Canada, in late 2013, Cibus and its partner BASF received PNT (plant with novel trait) approvals for herbicide-tolerant canola.
- An Expert Working Group on Novel Plant Breeding Techniques, appointed by the European Commission, concluded that Cibus' Rapid Trait Development System should be treated as mutagenesis and excluded from regulations applied to transgenes.
- Products like acrylamide-reduced potato and allergy-free peanut—with benefits that consumers can directly see—will bring links between the consumer and the science.
- The ARS is developing and refining genetic-engineering tools, including investigating technologies that utilize natural cellular mechanisms for genome repair that do not leave behind foreign DNA and precisely target genes of interest.

- There are two approaches for genetic engineering in farm animals:
  - — One is to modify the gene of interest in the genome of a somatic cell with either TALENs or CRISPRs.
  - — The second way is by direct modification of the gene of interest in the embryo genome, again using TALENs and CRISPRs.
- Recent reports indicate success in genetically engineering swine, cattle, and sheep by somatic cell nuclear transfer (SCNT) as well as direct embryo modification.
- To target the prion gene and, particularly, modify exon 3 in the prion gene, Cas9 nuclease was employed with a T7 promoter for *in vitro* transcription.
  - — Successful bi-allelic knock-outs, or modifications, were obtained at about 80 percent, by deletions as well as insertions.
  - — In some embryos, corrections were obtained by precise targeting and modification.
  - — Mono-allelic modifications were also effected.
- Insertion of a transgene into a particular locus has been achieved in a mammalian system.
  - — On the other hand, deletions occurred in some of the embryos.
- Putative knock-outs in swine embryos were achieved using NHEJ; this technology will be used to address animal-welfare issues.
- Pigs in particular have been modified with the CRISPR/Cas 9 system.
- There are possibilities of dual benefits where similar developmental issues in diseases apply to swine and humans.

Regulatory Issues–United States

- How will plant varieties created through gene targeting be regulated? Likely, each new variety will be considered on a case-by-case basis.
  - — The need for case-by-case evaluation of plants derived from gene targeting is warranted because of the range of modifications that can be created.
- Because genome engineering is a new approach to introduce genetic variation in plants, responsible regulation is required so that the technology can be best deployed for the public good.
- Policy issues associated with gene-editing in livestock and in biomedical research must be addressed for their real-world applications. Current deficiencies in regulatory oversight block enthusiasm for its adoption to agriculture.
- Regulatory pandering to public fears over food safety must change.
- Opinions rendered so far say that if the product does not contain pathogenic sequences, it should not be regulated.
- In the United States, it is encouraging to see that gene-editing of plants is being suggested as not requiring regulatory oversight. However, that concept remains under consideration *vis-à-vis* transgenic animals.

- It has been concluded by USDA-APHIS that the products of EXZACT™ Precision Technology fall outside their scope of regulation.
- The need to regulate plants developed through gene-editing techniques should be driven by the characteristics of the product (*i.e.* whether it is materially different from existing products present in food, feed or the environment) rather than by the method or process used to make that product.
- Because new plant-breeding technique (NPBT) approaches result in non-transgenic products, it is plausible that they may carry less perceived and actual risk, and that regulatory concerns will be minimal.
- It depends on whether you are looking at mutations versus addition of genes. One concern—especially with mutations—is harmonization in terms of what regulatory agencies are looking for.
- If regulatory oversight is developed for mutational products developed with the new technologies, it is to be hoped they will be harmonious and that required data will address questions of product and not process.
- Regulatory evaluation needs to be based on the safety of the product; if no risk is attendant on the product there should be little to no regulatory oversight.
- As of September 2014, APHIS has not been queried specifically about TALENS and CRISPRs/Cas9. However, in two letters—one on ZFN-1 and one on MN-1 breeding—APHIS stated that such plants were not subject to regulation because the techniques did not involve use of any plant pest at any stage.
- In light of these responses to letters of inquiry, USDA-APHIS appears poised to declare many—but not all—plants developed by the newer breeding techniques to be beyond its regulatory authority.
- In a recent scientific advisory panel (SAP) report, the SAP took a very precautionary approach to RNAi breeding and an affirmative view of the need for EPA to assert regulatory authority through FIFRA.
- FDA appears likely to assert that it will consider any animal modified by these newer breeding techniques also to be "new animal drugs."
- The basic message of a Venter report was that nothing in synthetic biology should avoid regulation.
- The advances in DNA editing are not yet changing the number or the type of applications for federal deregulation.
- Off-targeting is something we seek to avoid in genome editing.
- Fundamentally, we are interested in the phenotypes of these modified organisms, as opposed to what process was used in their production.
  - A paradigm shift from process to product would help to ensure a science-based evaluation of organisms developed through gene-editing technologies.

- It would be unwise to use the same regulatory process for DNA-edited crops as for GM crops. A better process should be adopted with correction of the problems caused by the current regulatory structure in the United States.
  - If there are potential food-safety risks, we should not adopt the FDA's voluntary process. A mandatory process is necessary to independently reassure the public regarding safety.

Regulatory Issues–Canada

- The Canadian Food Inspection Agency and Health Canada are committed to providing an efficient and appropriate level of regulatory oversight that encourages innovation while allowing Canadians to benefit from the advances brought by new technologies.
- The product-based approach allows the Canadian regulatory system to effectively adjust to any new developments in the science of plant breeding. Policy work is ongoing to help to ensure that guidance documents are available, as products of gene editing are brought forward for assessment.

Regulatory Issues–Europe

- There are several reasons to believe that the EU regulatory system will capture all newer breeding techniques.
- The European Food Safety Authority came to the conclusion that the aim of zinc-finger techniques is to integrate or exchange recombinant DNA and, therefore, it is comparable to transgenesis but more precise.
- The European Academies Science Advisory Council came to the following key conclusion and recommendation:
  - The trait and product not the technology in agriculture should be regulated, and the regulatory framework should be evidence-based.

Regulatory Issues–Global

- The Cartagena Protocol is likely to cover newer breeding techniques as regulated technologies.
- Without a paradigm change, poor and vulnerable populations will not have access to the new genetic-engineering technologies to enable them to raise their standards of living, improve their health and protect their environments.
- Differences in the regulation of new crops in different parts of the world will cause asynchrony in the approval of such crops. Consequently, global discussion concerning regulation of NPBTs is necessary to achieve synchronized and evidence-based governance.
- It is crucial for companies to be certain at the outset that their investments will not be in vain and that their future products will not be subject to the uncertain outcome of politicized regulatory procedures, as is the case with GMOs.

- When an organism does not contain recombinant DNA, it should not be risk assessed and regulated as a GMO.
- Flexibility is important—flexibility to learn and then to adjust as needs be and as new technologies come along.
  - Flexibility in the policy context is important also.
  - A universal, standardized set of definitions should be developed and utilized to mitigate confusion about the regulation, adoption, and legislation surrounding gene-editing technologies and their resulting products.
  - At issue is mutation versus gene addition. Part of the concern—especially with mutations—is harmonization in terms of what regulatory agencies are looking for.
  - If regulatory oversight is developed for mutational products developed with these technologies, it is to be hoped they will be harmonious and that required data will address questions of product and not process.
  - Regulatory evaluation needs to be based on the safety of the product; if no risk is attendant on the product there should be little to no regulatory oversight.

General Considerations

- The outcomes of our genetic modifications may be made even more precise, more controlled and more predictable so as to minimize concerns about off-target effects.
- Communication of science is essential, not only to the public but, as scientists and opinion leaders, to our communities as well as to the government.
- How should scientists address the public on the subject of gene-edited crops and livestock?
- Many people attending this conference can be thought leaders within their communities. Are there non-technical thought leaders who might be receptive to technical arguments?
- Gene editing is affected by the target sequence and reagent, and is not always precise. Appropriate standards are needed for determining whether or not there are off-target effects that affect the safety of the product:
  - In general, off-target effects are rather infrequent. Reasonable standards may be set for the types of products that are released. We have good genome sequences for most of the plants and animals with which we work. For a modest amount of money, we could determine the genome sequence in the plant or animal we wish to release to show that, in fact, the only mutation is the one actually wanted.
- Enzymes and transcription factors from different organisms have different efficiencies. Do these technologies allow for closely related enzymes and

transcription factors, differing by one or two amino acids at the active site, to be precisely modified, effectively mutagenizing a low-efficiency enzyme or transcription factor for greater efficiency?

— We can go in and make pretty much any modification we want in any gene we want whether it has a transcription factor or not. That capacity is currently there. As we look towards the future, screening *in vivo* for variations of interest is certainly a possibility.

- This conference is an attempt to assemble the available information in one place to see where we go from here into the future. Everybody wants the best outcome, For the public, the consumers, the industry, the researchers—everyone—the goal is the same.
- We have seen different sides of the issues from basic science to regulatory aspects to public acceptance or non-acceptance of this technology.
- We in the science community have to be available to speak about these issues and tell things as they are.
- Flexibility is important—flexibility to learn and then to adjust as needs be and as new technologies come along.
- By 2050, the demand for staple food crops alone will require yield increases of nearly 80%.
- Technologies that complement traditional management and breeding, but dramatically accelerate production and testing of improved crops, are in critical demand.
- Just as improved plant breeding and crop management spawned the Green Revolution in the 1960s, so too could these new technologies transform crop improvement in this generation.
- The mission of the Iowa State University Crop Bioengineering Consortium (CBC) is to deploy innovative, transformative genome-engineering technologies that identify, validate, and rapidly, but precisely, integrate strategically important traits and underlying genes into key crop plants.
- The CBC is establishing a platform comprising: active gene discovery and validation; incorporation of target gene modifications into crop plants using new NPBT approaches and novel delivery methods; trait verification and integration; and evaluation of regulatory, economic, environmental and societal impacts of the technology and the resulting traits.
- The time is ripe to launch a public-sector infrastructure for rapid, precise crop bioengineering.
- The CBC is developing high-throughput processes for all stages of the genome-engineering pathway, beginning with development of software for the prediction of CRISPR-editing targets for any gene in a variety of genomes.

- We could feed another 4 billion people if we could figure out how not to waste the food we produce, and a valid discussion is to be had about how much energy should go into production of various non-food agricultural products. However, there remains a need to produce more food.
  - There is no single solution to producing more food; the solutions include irrigation and pesticide application, and farming-equipment availability, along with improved breeding techniques.
  - Part of the solution is educational in terms of sharing science across the world.
- As we encounter new breeding technologies, especially site-directed gene-editing techniques, there would appear to be a window of opportunity to reframe public understanding of genetic engineering in agriculture.
- Properly answering *why are you doing this* is important for the public because many suspect that somebody is tinkering with something because they can do it rather than for a good reason.
  - If things are done by a multinational corporation, consumers are more hesitant than if they are done by a small company or by a public university.
- There is no need to regulate when there is no safety issue.
- A few articles have been published in scientific journals about gene-editing techniques and how they may be perceived and regulated. The consensus was that it would depend on whether exogenous DNA or endogenous DNA is involved. However, in practice, it may not be so simple.
- When consumers look at these new technologies, they are unlikely to appraise them simply on whether they contain introduced DNA. The situation is more complicated. They are going to consider, *inter alia*, the breeding method, the specifics of the trait, and the level of knowledge about the technique.
  - The factor that will influence consumer acceptance most is safety, and consumers will want to know who is ensuring safety.
  - A product in the public domain is a lot more acceptable to many consumers than if it's patent-protected.
- Consumers will need to know what scientists are doing and will need to have answers that are scientifically accurate and also understandable. The public does not want to be "dumbed down" to.
- Prevalent issues are:
  - What are the potential benefits and who benefits—who are the winners and who are the losers?
  - What is "natural"? We don't have a scientific definition, but, clearly, the public's perception of what is natural will come into play. The public may say that some things are natural that scientists would disagree with.

- If there are potential risks, then there should be oversight. Questions are:
  - What risks come from the process used?
  - What risks come from the products made from that process?
  - How does the risk profile compare to other agricultural breeding techniques and products?
- It is important to bear in mind that risk is not absolute, it's relative.

Genetically Engineered (GM) Plants and Animals

Uses

- Genetic engineering using recombinant-DNA vectors versus genome editing using site-specific DNAases: the gain in precision between the two methods is a factor of ten million.
- In the United States, not a single animal engineered for food production has been approved by the US Food and Drug Administration (FDA), which regulates GM animals.
- Transgenic technologies were greeted with more concern than enthusiasm by the general public and, especially, by several NGOs. The concerns focused on four areas:
  - Health effects due to the *un-naturalness* of products the modified genome might encode;
  - Environmental effects due to uncontrolled release of transgenes (*i.e.* GM animals) and reduced diversity of natural genomes;
  - Social concerns that huge corporations would have undue influence over diets; and
  - Moral concerns that were summed up by the phrase "playing God."

Regulatory Issues/United States

- The issue of huge corporations dominating the availability of GM products is, in large part, a direct consequence of the cumbersome regulatory processes.
- The mistake that was made in the United States, back in the 1980s, was to elect to use existing legislation. Although useful in the short term, this has been disastrous in the long term.
  - The United States did not adopt biotechnology-specific legislation. Rather, the US government developed a coordinated framework allowing the three primary administrative agencies [Department of Agriculture (USDA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA)] to develop policies under existing statutory authorities about regulating recombinant-DNA techniques.

- There is general agreement among regulatory agencies internationally that regulatory oversight should be reduced, but no one has proposed what the necessary data might be. The trend of requirement of more and more data should be reversed.
- The USDA Animal Plant Health Inspection Service (APHIS) created a category called a "regulated article" under the Plant Protection Act. EPA created a category called a "plant-incorporated protectant" (PIP) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FDA created a voluntary consultation process for foods derived from biotechnology and later declared that all animals derived from biotechnology are "new drugs" under the Federal Food Drug & Cosmetic Act.
- USDA-APHIS has approved 96 petitions for non-regulated status.
  - USDA-APHIS now takes nearly 5 years to make a decision with a regulatory cost per trait of up to $34 million.
- Despite many successful and needed crop transformations by public-sector scientists, only one public-sector crop has ever achieved regulatory approval and commercial release: the virus-resistant papaya for Hawaii. APHIS has also approved a USDA-ARS virus-resistant plum, but EPA pesticide-labeling requirements have prevented its commercial release.
- EPA defined genetically-modified microorganisms (GMMs) as regulated "new chemicals" under the Toxic Substances Control Act (TSCA). Since then, EPA has approved one GMM for commercial use.
- FDA has not approved a single commercial release of animal agricultural biotechnology.
- The US regulatory system has not responded to the real-world evidence of benefits without novel harms. The US regulatory system could be improved through several efforts within the power of the regulatory agencies such as:
  - Adopting categorical exclusions;
  - Focusing anew on product, not process;
  - Exercising agency discretion to decline invoking new terms and new definitions that expand regulatory power; and
  - Creating a culture of facilitating innovation, science and technology.
- Regulatory officials at the three agencies regularly communicate and exchange information to ensure that any safety or regulatory issues that may arise are appropriately resolved.
- USDA-APHIS biotech regulations provide a petition process for the determination of non-regulated status.
- USDA-APHIS evaluates a variety of issues including the potential for plant-pest risk; disease and pest susceptibilities; the expression of gene products, new

enzymes, or changes to plant metabolism; weediness and impact on sexually compatible plants; agricultural or cultivation practices; effects on non-target organisms; and the potential for gene transfer to other types of organisms.

- The current regulations under 7 CFR 340[2] do not apply to all GM organisms or even all GM plants. For example, plants transformed by particle bombardment with DNA that is not derived from a plant pest do not trigger the regulations under 7 CFR 340.
- Although APHIS is not in a position to discuss agency deliberations on the proposed rule[3] until closeout, a document describes overarching principles for the regulation and oversight of the products of emerging technologies. These principles are described in a memo by the White House Office of Science and Technology Policy, partially as follows:
  - When no significant oversight issue—based on a sufficiently distinguishing attribute of the technology or the relevant application can be identified—agencies should consider the option not to regulate.
  - Decisions should be based on the best reasonably obtainable scientific, technical, economic, and other information, within the boundaries of the authorities and mandates of each agency.
  - Public participation is important for promoting accountability, for improving decisions, for increasing trust, and for ensuring that officials have access to widely dispersed information.
  - The federal government should actively communicate information to the public regarding the potential benefits and risks associated with new technologies.
  - The benefits of regulation should justify the costs (to the extent permitted by law and recognizing the relevance of uncertainty and the limits of quantification and monetary equivalents).
  - Federal regulation and oversight should provide sufficient flexibility to accommodate new evidence and learning and to take into account the evolving nature of information related to emerging technologies and their applications.
  - Risk assessment should be distinguished from risk management.
  - Federal agencies should seek to coordinate with one another, with state authorities, and with stakeholders to address the breadth of issues.
- Organisms engineered without plant-pest sequences may not fall under the 7 CFR 340 regulations.

[2]Regulation of organisms and products, altered or produced through genetic engineering, that are plant pests or for which there is reason to believe are plant pests.

[3]In early 2015, APHIS announced that it is abandoning the proposed rule, after several years' consideration, and will start over to produce a new rule.

- The USDA is not involved in oversight once the product has been deregulated. Development of insect resistance to *Bt* and/or weed resistance to herbicide, involves the EPA.
- Good stewardship requires monitoring for weeds that are becoming resistant and developing a rapid response to rectify that situation.
- Evaluators look for potential allergenic epitopes in proteins. If new information comes to light, they need to be told.
- USDA has a staff of about eighty on the regulatory side, about two-thirds of whom are scientists.

Regulatory Issues/Canada

- Canada takes a product-based approach to assessing plants with novel traits (PNTs) for use as food, as feed, and for release into the Canadian environment.
  - — The trigger for regulation in all cases is based on novelty.
  - — The regulatory trigger is not identical for novel foods, novel feeds, and PNTs. It is, therefore, necessary to consider whether a product may be novel under each relevant set of regulations.
- Completion of the regulatory process in Canada takes twenty months on average. Twelve to twenty-four months is typical.
- In Canada, only a half-dozen people are employed in regulatory agencies
- Once something is approved it is considered to be the same as any other cultivar that's out there.
  - — On the organic side, neighbors are encouraged to cooperate.

Regulatory Issues/Europe

- Requests to place a single event on the European market cost somewhere between 15 and 50 million euros.
- The European regulation provides consent for only 10 years. During these 10 years, monitoring is mandatory.

Regulatory Issues/Global

- Globally, regulatory oversight of biotech products is a time-consuming and expensive endeavor, estimated at $35 million per trait with an average of six years for regulatory approval/deregulation.
- At the international level, 168 countries have ratified the Cartagena Protocol on Biosafety, which governs the transboundary movement of "living modified organisms" (LMMs) from "modern biotechnology."
- Harmonization of GM regulations will increase international trade.
  - — In the international arena, harmonized regulations can result, detrimentally, in the lowest common denominator.

— Some scientists support, and strongly urge, international harmonization of requirements of scientific data and risk-analysis frameworks.

- There's a fairly large literature of poorly done anti-GM studies.

Labeling

- Why are GM crops examined so closely when food supplements are largely ignored?
- The information on food labels should have a bearing with regard to consumer safety.
- Labeling of GM foods has been reshaped by the protest industry over time, from a science issue to a choice issue.
- The protest industry is intent on using labeling to drive agricultural biotechnology out of the market
  - — It is allied with the organic industry, which sees this as a way of increasing their market share significantly.
- Those who are aligned against GM technology and foods derived from GM crops will use labeling as the next step in their campaign to denigrate and stigmatize this technology.
- In Europe, the advent of labeling meant that the processor simply stopped accessing any food that had an ingredient that required the food to be labeled, and it has had a tremendously detrimental impact.
- The purpose of a label is to provide effective, clear information to consumers so that they have safe foods.
- CSPI[4] does not support mandatory government-imposed labels except in situations where a safety or nutritional issue dictates it.
- The distinctions Europe makes between a food made *with* a GMO and a food made *from* a GMO should be dropped.
- The leading enzyme company, Novozymes of Denmark, produces many enzymes and if you were to label every food produced with those enzymes, it would entail almost 100% and become irrelevant.
- Across the country, numerous state and local governments have enacted, or are considering, laws that impact the cultivation, use, and labeling of GM plants. These laws are best described in three categories:
  - — Laws that ban the cultivation of GM plants;
  - — Laws that regulate the handling of GM plants; and
  - — Laws that impose disclosure requirements on the sale of GM plants, such as food labeling.

[4]Center for Science in the Public Interest.

- There are two types of labeling laws: those that apply to food and those that apply to seed.
- Only four states (to September 2014) have passed GM-food-labeling laws: Alaska, Connecticut, Maine and Vermont.
- Several states have enacted laws that require labeling of GM seed.
- In Vermont, a group of plaintiffs, led by the Grocery Manufacturers Association, is challenging the state's GM-food-labeling law alleging that the law violates:
  - The First Amendment's protection against forced commercial speech in requiring a label;
  - The First Amendment's protection against restricting commercial speech for preventing the use of the term "all natural" on food required to be labeled;
  - The Fifth Amendment's due process clause for containing vague terms regarding the restriction of using terms "similar" to "all natural";
  - The Commerce Clause for imposing unreasonable burdens on manufactures outside of Vermont; and
  - The Supremacy Clause on account of the fact that the law conflicts with federal law.
- If there is to be labeling *vis-à-vis* GM ingredients in foods, it should be in terms of stating their *absence*.

General Considerations

- Over the past 5 years, two obvious changes have been occurring: Of incoming freshmen, only 2 percent believe that they *don't* eat GM food; ninety-eight percent think either they are, or they might be, eating GM foods, and it doesn't concern them in the slightest. Secondly, most of them feel that regulatory policies fail to take advantage of recent developments, but they also feel that regulatory agencies can be trusted to save them.
- China needs fish for human consumption, but has deferred to the United States' approval of GM salmon, as have regulators in other countries who are waiting for the United States to do it the right way.
- The cost of DNA sequencing has decreased dramatically over the past two decades due to technological progress.
- Regarding transgenic techniques, the location at which the transgene lands is random.
- Biotechnology is largely in its infancy in terms of ability to modify algal genomes, especially in production-type algae.
- On the plant side, anti-GM rhetoric has been relatively quiet recently.
  - Greenpeace has been good at scaring the public about GM products; they can say anything on the Internet without proof.
  - There has been less resistance to *Bt* cotton because it isn't eaten.

- NABC's conference in 2013, on fruits and vegetables, focused in on three or four examples of consumer benefits. The non-browning Arctic apple was one of those and it seemed to be moving fairly quickly through the regulatory system; it's out for comment at the moment (October 2014).[5] Another example was *Bt* sweet corn, which doesn't require spraying with insecticide. Simplot's Innate™ potato technology is another good example, as is the (GM) means of tackling citrus-greening disease.
- The rapid and continuing global adoption of modern agricultural biotechnology has been encumbered by steadily increasing public anxiety, although scientists and regulators continually point to the weight of evidence that GM crops pose negligible risks to human health and the environment, *i.e.* GM crops are equivalent to their non-GM counterparts.
  - — Despite nearly two decades of safe use worldwide, large segments of the public continue to express concerns regarding foods derived from modern biotechnology.
  - — We must reframe genetic engineering using these new technologies in agriculture in a way that more effectively connects with the public.
- Traditional breeding, whether by farmers or by scientists, has been either unregulated or lightly regulated, primarily to assure seed purity and efficacy. Recombinant-DNA techniques have been carefully regulated domestically and internationally. The regulatory classifications of the newer techniques are still in debate and have much uncertainty.
- It's the retailer's job to understand customers' perceptions because their perceptions are their reality, whether or not they are based on fact.
  - — We have to listen to consumers and try to understand their concerns and their perceptions in order to gain their trust.
- Transparency without trust is useless, and trust doesn't happen overnight. You can't demand it. You have to earn it and you have to build it.
- The very large majority of customers' expressed concerns are focused on product recalls. By comparison, concerns over GMOs are few in number, and concerns over animal welfare are fewer still.
- At CSPI, they have looked at the data behind GM crops grown in the United States and concluded that foods made from those crops are safe to eat.
  - — There are benefits from those crops, to farmers and to the environment, although not necessarily any direct benefits to consumers. Those products need to be assessed on a case-by-case basis.
- Uses for agricultural biotechnology must be sustainable so that they are there for future generations of farmers.

[5]In early 2015, USDA approved the Arctic apple, which FDA is reviewing.

- Regarding consumers and food, the primary concerns are safety, healthfulness and nutrition. Taste is important, as are tradition and religious significance.
- Some consumers know a lot of about science, whereas some don't know much at all.
  - Consumers receive information from opinion leaders whose viewpoints they consider important and who may be with NGOs or universities.
  - However, for some consumers, if they believe something, scientific data and reasoned argument may not change their minds.
- International consensus indicates that GM crops are safe and beneficial.
- Selected breeding has been beneficial for the agricultural community with the production of superior animals with desirable production traits.
  - On the other hand, frequently, along with desirable traits, undesirable traits will segregate, such as susceptibility to diseases.
- A negative aspect of selective breeding is the length of time that it takes to achieve genotypic improvement; for cattle it can be about a quarter century.