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Guidance for regulated biotech trials in the U.S.

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Guidance for regulated biotech trials in the U.S.

by

Lisa Baker

A creative component submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

MASTERS in AGRONOMY

Major: Agronomy

Program of Study Committee:
Allen Knapp, Major Professor
Walter Suza

Iowa State University

Ames, Iowa

2020

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DEDICATION

I would like to dedicate this dissertation and my degree to my husband, Thomas Baker. He is my biggest champion and has thought I could do this even when I did not. He is also a realist in helping me to control my desire to overload myself at times to protect my sanity and his. He is my best friend and has my love, and thanks for his support through this process.

When you start the program, it isn't just you, but your whole family is involved. Everyone will be impacted by your stress level at times and the amount of time you put in the program. Tom has always been willing to help in any way and took on a lot of additional responsibility with our move and things around the house to help me complete my degree and this dissertation.

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NOMENCLATURE

GMO	Genetically Modified Object
GM	Genetically Modified
USDA	United States Department of Agriculture
FDA	Food and Drug Administration
EPA	Environmental Protection Agency
BRS	Biotechnology Regulatory Services
APHIS	Animal and Plant Health Inspection Service

Biotech materials- any materials produced using biotechnology, in particular

GMOs

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I would like to thank Dawn Miller. She was kind enough to notice the times I was struggling with this project and offered suggestions along with speaking to Dr. Knapp. Without her assistance, I would not be at this point. Dawn is a true champion of the agronomy program and Iowa State University.

Deborah Burns was essential to my completion of the project. She was a writing consultant, friend, confidant, teacher, and mentor. Without her assistance, I would not be done. She was able to help me see and understand my leaps in thought, as it can be difficult to create a paper on a topic you have worked in for years and been an expert. I think everyone knows what I am talking about, and Deb helped me to see and understand the areas where that isn't true.

I would also like to thank my friends, colleagues, peers, and professors for my experience at IA State. This is a wonderful program, and without its flexibility, I would not have been able to complete my Masters in Agronomy.

ABSTRACT

This creative component provides an overview of what must be done to comply with U.S. regulations for conducting regulated biotech trials in a field setting which are different than the requirements for contained facility studies (lab or greenhouse). Many risks must be assessed and addressed by an organization wishing to conduct the regulated biotech trials, and the USDA must approve of these methods to address risk.

The audience for this creative component is those with a background in agriculture and knowledge of biotech materials. The information addresses how to manage regulated biotech trials per USDA requirements in the United States but will not provide a background on the creation of biotech materials or how products are deregulated or approved for commercial sale. This creative component will be helpful for anyone considering a role in compliance. It is important to keep in mind this creative component outlines what to do but not how to do it. The compliance processes are up to each organization to address. This paper represents a snapshot in time as regulations continue to change.

1. INTRODUCTION:

Farmers endeavor to produce the highest economic yield possible. Many input systems are available to help farmers reach their yield goals. These crop inputs include hybrid seed, fertilizers, irrigation, precision farming machinery, and biotechnology (biotech) crops. Biotech crops are popular with growers due to their potential to save them time and other resources while increasing yield. Biotech crops have also faced scrutiny over their cost, potential for inducing pest resistance, possible health concerns. For instance, could the toxins they produce adversely affect human health.

Biotech crops, also known as genetically modified (G.M.), were first commercialized and sold in the U.S. in 1996, with 1.7 million hectares planted (James, 2014). By the end of 2014, growers planted over 180 million hectares. The rate of adoption for genetically modified crops has increased across multiple crops and with different traits or attributes over the years (Fig. 1). There were periods of sharp increases in acres planted in the late 1990's, but now we are near saturation as 80 to 95% of the acres planted are biotech (James, 2014).

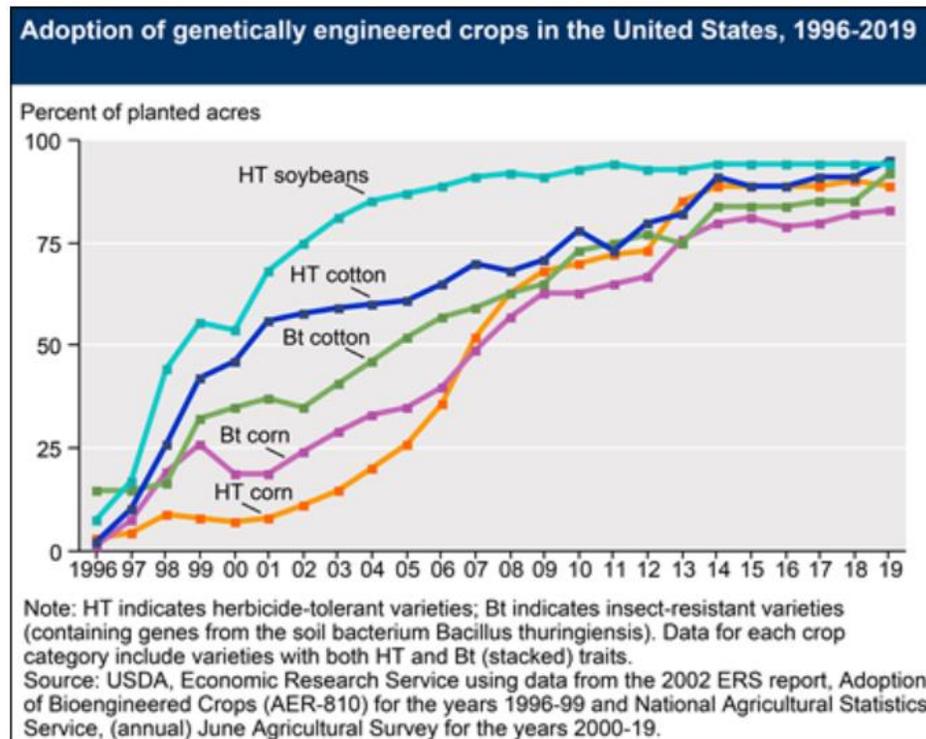


Fig 1 Adoption of genetically modified crops in the United States, 1996-2016 (USDA ERS, 2019).

Herbicide-tolerant (HT) varieties are available for cotton, corn, and soybeans (Fig. 1). Some of the familiar HT products are RoundUp® Ready (tolerance to glyphosate) and Enlist® (tolerance to 2,4-D). These HT crops allow the farmer to plant seed carrying the herbicide tolerance trait, so the resultant crop can be sprayed with the herbicide to eliminate weeds that are susceptible to the herbicide without killing the HT crop. Herbicide-tolerant crops are widely accepted by farmers and seen as time-saving compared to many cultural weed control practices. However, there are concerns that GM crops can also cause an over-reliance on herbicide use, which leads to resistance management issues. The other acronym seen in Figure 1 is *Bt*, *Bacillus thuringiensis*, this is a bacterial species known for its insecticidal properties. This character was discovered in Japan in 1901 (Roh, et al. 2007). The *Bt* bacterium produces Cry proteins, and when ingested, the Cry proteins are activated in the midgut of insects such as corn root worm. The activation of the Cry protein makes the toxin

lethal to certain insects, causing cells in the lining of the gut to swell and burst. As a result, the insect will stop feeding soon after the ingestion of Cry proteins. Next the insect becomes paralyzed and dies. Cry proteins are highly specific; they are only effective on certain insects. Thus, beneficial insects are not affected by ingesting them (Roh et al., 2007).

The USDA, FDA, and EPA oversee the specificity and safety of biotech crops. Collectively, these three agencies are known as the Coordinated Framework and regulate biotech crops before commercialization. The seed or grain which will display a new phenotype is regulated by the USDA, while the FDA is consulted with voluntarily; and the EPA has a different application and review process than the USDA and only regulates insect-resistant biotech crops. The differences in how and what the agencies regulate can confuse consumers and generate concerns about transparency by the government.

Farmers continue to face numerous biotic and abiotic stressors that limit productivity. So, there is still a need for the research, development, and commercialization of additional biotech crops. In the U.S., this means there will be interactions with numerous government agencies as approvals for the product are sought. One aspect of this approval is the data generated in field studies, and since these products are regulated, rules must be followed for them to be planted and studied in the field. This module is designed to help a person creating a compliance program for their company.

U.S. Regulations

Many Agriculture companies such as Bayer, Corteva, or Chem China (Syngenta), create genetically modified crops. They may collaborate with smaller companies or

universities in the discovery, testing, and creation of the product. Relationships between universities or smaller companies may result in the discovery of a gene with efficacy against a particular pest of economic concern in a region, resulting in a new product. These collaborations may require the parties to sign a confidentiality agreement and other documents defining working arrangements for future studies of the product. These agreements may cover future greenhouse, lab, or field testing. The larger company may purchase the product, or it could be co-produced, and the legal departments of the organizations will determine the contract specifics on the production and sale of the product. The timelines for these contracts can vary depending on the complexity of the agreement. The contract will typically contain detailed information regarding terms of ownership, use, publishing and compensation. Many large organizations will utilize a master contract as a template to ensure that all regulatory compliance, stewardship, quality testing and trial management factors are addressed and consistent across the organization. Many universities collaborate with agriculture companies because of the resources and the systems these companies have in place to manage the trials. As a result, liability shifts to the ag company from the university, as the holder of the permit or primary manager of the study.

New products go through many stages of testing. These may originate as greenhouse or lab studies done as a proof a concept, which will define the efficacy of the new product.

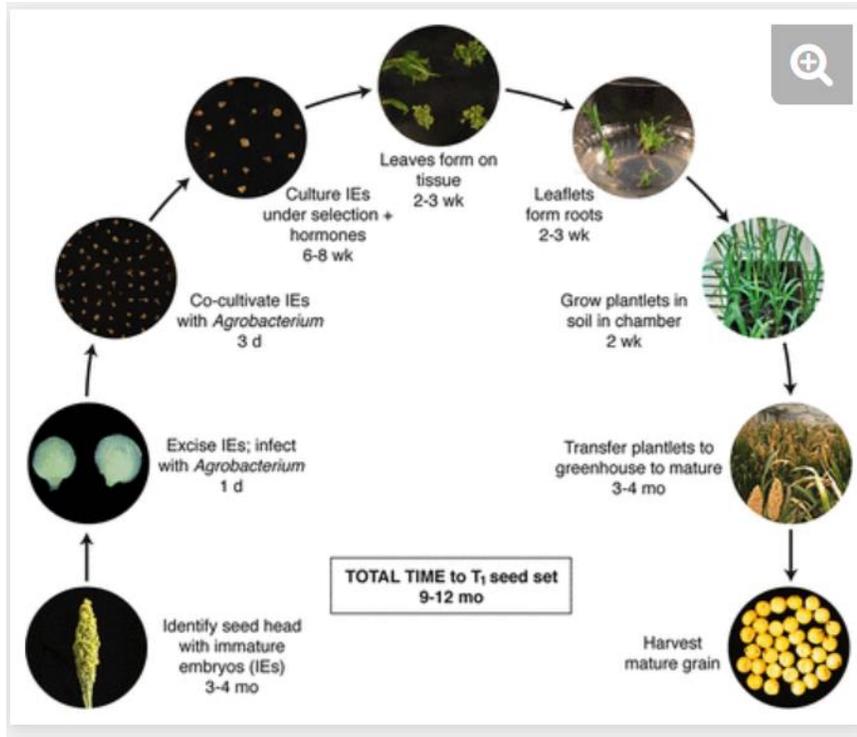


Fig 2. This is an outline of the timeline for transformation, given in d (days), wk (weeks) and mo (months). While the regeneration time will vary the steps outlined are similar across many crops. The process begins with the generation of donor plants through the harvesting of grain or mature seed from regenerated plants (F. Altpeter, et. al, 2016).

Many studies originate as dose-response or feeding studies done in the lab and then move to greenhouse studies in the plant of interest or a model species. Once the initial testing in the lab or greenhouse is complete and enough seed is produced, it is time to initiate field studies. The data from the lab and greenhouse studies support the proof of concept data for the product; however, this does not show how the product reacts in a “real world” setting, as these studies are based on the ideal environments of the lab or greenhouse. Since these are not commercial products, the crop is regulated, and government permissions are needed to plant these crops in field settings. The regulations and rules provided by government agencies, provide the basis for the standardization of processes to conduct these trials by biotech companies.

How it started

In 1984, a series of interagency working groups began reviewing the laws applicable to the oversight of biotechnology. The review resulted in the formalization of regulatory status and policies (Wolt and Wolf, 2018). The Office of Science and Technology Policy (OSTP) released the Coordinated Framework for Regulation of Biotechnology, which created the regulatory responsibilities, lead agencies, and jurisdiction relying on existing laws for oversight of biotechnology (OSTP, 1986). The Coordinated Framework shows “the overall thrust of the regulatory response to biotechnology may be termed a minimalist, cost-effective, priority-driven approach requiring burden of proof that regulation is warranted” (Krimsky and Wrubel, 1996).

The most significant regulatory approach to emerge from the Coordinated Framework was a change from oversight based on the process used in biotechnology to the product of the biotechnology process (Wolf and Wolt, 2018). This allowed the Agency to focus on the risk of the actual product and not how it was made. For example, the agrobacterium used as the transformation method is not where the risk is, but rather on the product, such as glyphosate resistant corn. The Coordinated Framework continues to evolve in response to changes and advances in biotechnology innovation, knowledge, and improved understanding. To date the evolution has occurred through regulatory rulemaking and changes in the regulatory guidelines rather than implementing new or revised legal statutes (Wolf and Wolt, 2018).

In 1992, the Coordinated Framework clarified how regulatory authority should be conducted when there is latitude as to the discretion that may be taken by the implementing agency (OSTP, 1992). This means the Agency has the power to determine how to handle or implement change. This update used precise language to emphasize that regulations should

address only those risks that are “real and significant rather than hypothetical or remote” and provide evidence the risk is unreasonable (Wolt and Wolf, 2018). So, the government could not regulate for things that it did not have sufficient knowledge of and more importantly, for circumstances that could or would not happen. In 2015, efforts to update the regulatory system for biotechnology were proposed; however, there was no major change brought forth to update the goals and plans in the Coordinated Framework (Wolf and Wolt, 2018).

2.2 U.S. Food and Drug Administration

In 1992, the Food and Drug Administration issued a policy statement on foods derived from plants developed by biotechnology. The FDA clarified their product-oriented positions that these foods were substantially equivalent to foods already for sale and except for those instances when the “objective characteristics of the substance raise questions of safety sufficient to warrant formal premarket review,” no defined regulatory action was needed by the FDA (FDA, 1992). In 2001, the FDA issued a proposed rule to mandate developers submit a scientific and regulatory assessment of a biotech food before it is marketed (US FDA, 2001). However, there has been no action on this rule, so the FDA continues to follow its voluntary consultation process for biotech products. The FDA has provided guidance to industry on its consultation procedures, early food safety evaluation and voluntary labeling standards for foods from G.M. plants (FDA, 2018a). It regulates under laws including the Food, Drug, and Cosmetic Act (FDCA), and the Public Health Service Act (PHS), which oversee the safety of most foods and drugs for humans and animals, including those produced using biotechnology (Wolf and Wolt, 2018).

2.3 Environmental Protection Agency

The U.S. Environmental Protection Agency (EPA) has broad authority of direct and indirect bearing on biotechnology products. The primary statutes under which the EPA

exercises authority are the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), and the Federal Food, Drug, and Cosmetics Act (FFDCA). Crops which are genetically modified to express plant incorporated protectants (PIPs) are considered with respect to their pesticidal protein and not the modified plant. Proteins from *Bt*s, which provide insect resistance are examples of PIPs. Along with PIPs, the EPA indirectly reviews G.M. crops which provide herbicide tolerance by weighing the risk of exposure to the herbicide used to manage the crop. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA regulates pesticides. Under section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA), EPA establishes the amount of pesticide chemical residues that may be present in food. Under the Toxic Substances Control Act (TSCA) and regulations implementing that statute, EPA currently regulates biotechnology products that are new microorganisms not specifically excluded by the statute (generally those regulated by other statutes) (Wolf and Wolt, 2018).

Within the USDA, the Animal and Plant Health Inspection Service (APHIS) is responsible for protecting agriculture from pests and disease. USDA-APHIS regulates organisms and products that are known or suspected to be plant pests or to pose a plant pest risk, including those that have been produced through genetic modification or are classified as invasive species. These are called “regulated articles.” USDA-APHIS regulates the import, handling, interstate movement, and release into the environment of regulated organisms that are products of biotechnology, including organisms undergoing confined experimental use or field trials. Regulated articles are reviewed to ensure that, under the proposed conditions of use, they do not present a plant pest risk through ensuring appropriate handling, confinement and disposal (Wolf and Wolt, 2018).

The Plant Protection Act (PPA) provides the framework for the oversight of G.M. organisms to protect plant health by the (USDA) that may post a pest risk to plants (CFR7 part 340). Starting in 2008, the USDA initiated an effort to institute new rules for G.M. organisms to include parts of the Noxious Weed Act of 1972 along with the PPA to simplify the process for determination of the regulatory status of certain G.M. organisms (USDA, 2008). This proposal was withdrawn in 2015 following a long public comment period, which allowed the USDA to engage in new stakeholder communication on APHIS biotechnology regulations and to start a program, Environmental Impact Statement (EIS) (USDA, 2016 a, b). Under the Animal Health Protection Act (AHPA) and the Plant Protection Act (PPA), USDA regulates products of biotechnology that may pose a risk to agricultural plant and animal health. Under the Virus-Serum-Toxin Act (VSTA), USDA has regulatory oversight over products of biotechnology that are included in veterinary biologics, and ensures that veterinary biologics are pure, safe, potent and effective (Wolt and Wolf, 2018).

In addition, the Food Safety and Inspection Service (FSIS) is the public health agency in USDA that is responsible for ensuring that the United States' commercial supply of meat, poultry, egg products, and fish of the Order Siluriformes is safe, wholesome, and correctly labeled. Under the Federal Meat Inspection Act (FMIA), Poultry Products Inspection Act (PPIA), and Egg Products Inspection Act (EPIA), FSIS inspects all meat, poultry, and processed egg products in interstate commerce. FSIS uses these authorities to regulate products under its jurisdiction, including those derived using genetic engineering (Wolt and Wolf, 2018).

With each Agency focusing on its own area of risk and how it will be evaluated, the confusion of the consumer increases, as noted earlier. This leads to many questions and

opens the door to questions on which Agency is right or doing a better job. Rather than seeing this as a way to make sure all of the risks are studied by the most qualified group, it becomes a question of why they are doing things differently.

Overall Authority

Agencies working within the Coordinated Framework must address regulatory processes and determinations of regulatory status for productions of biotechnology through federal statutes which have broad authority, which means they have jurisdiction over a large range or selection of topics. For instance, the EPA has jurisdiction over drinking water purity, and some facets of biotech crops. An aspect of these overarching authorities is the ability for broader public involvement than is generally experienced under the Coordinated Framework. The USDA has a public comment period for many of its decisions on regulated biotech to allow for a broader public opinion (Wolt and Wolf, 2018). Other agencies, such as, the Department for Veterans Affairs provide healthcare services to veterans, while other agencies such as the Department of Defense coordinate and supervise functions of the government related to national security and the Armed Forces of the United States, which are large areas of focus yet a narrow scope to operate within. These agencies will also act primarily independently of each other and do not see public opinion on decisions they are making.

The National Environmental Protection Act (NEPA) mandates that federal agencies take a “hard look” at how a regulatory action may affect the human environment (Department of the Interior, 2004). Under NEPA, significant environmental impact of an action must be revealed to the public prior to the decision being made on regulatory status or action taken, but it does not dictate the nature of the action or decision based on the analysis

conducted (Bean, 2009). The agency creates an environmental assessment (E.A.) and if the base determination is a Finding of no Significant Impact (FONSI) there is no need for additional analysis. If the provisional determination by the agency is that the proposed action or determination may significantly impact the human environment, which is the area a human lives in, humans and the environment interact and adapt to one another, then an environmental impact statement (E.I.S.) is required. The E.I.S outlines the proposed action or determination and any alternatives and weighs the environmental impact of each in arriving at their final action or decision. The process and need for NEPA is provided by the Council on Environmental Quality (CEQ) for the agencies (Wolt and Wolf, 2018).

The Endangered Species Act (16 USC part 35, United States Code 2012) mandates federal agencies consider direct and indirect impacts of actions or decisions they take on endangered species and their critical habitat. The Endangered Species Act is administered by the U.S. Fish and Wildlife Service and the National Marine Fisheries Service. Agencies conduct their own assessment regarding endangered species. If they find there will be “no effect” from the action or decision, then no further action is needed, which means the agency may conduct or go forward with the action, while ensuring they do not deviate from their plan or note any unforeseen impacts; in cases where there may be an effect the agency must consult with FWS and/or NMFS to determine if the effect is “likely.” If the impact is “likely” then FWS or NMFS will conduct an assessment, and they will determine if the organism or its habitat are in jeopardy. This leads to a decision by the applicant, can they adjust or changes to avoid the “likely” impact or if the agency moves forward and finds a like impact, the applicant must propose actions to limit the impact of their action or they may have to determine they cannot go forward at this time. The Applicant could also push back

and try to go forward knowing there is likely impact, but that would be very risky, and most would not do this due to the implications to the environment and negative impact on their reputation and standing.

Federal statutes applied under the Coordinated Framework have not led to any findings of likely effect for G.M. crops and, formal interagency discussions regarding this have not taken place, as a result (NASEM, 2017). A problematic aspect of the ESA process for biotech products is that assessments for G.M. organisms under the Coordinated Framework allow some reasonable degree of risk, while ESA determinations are concerned with loss of a single individual. Attempts to connect or coordinate the endangered species assessment approaches used across agencies have been made (NRC, 2013), but have not yet been applied to biotech products (Wolf and Wolt, 2018). Which can lead to chaos and in the absence of information the public will make up its own information or follow and trust in information that is not correct or flawed because it is at least something to follow. This chaos leads to lawsuits of the government, public mistrust of government decisions, and the thought that the government has been bought by big business.

Along with each of the Agencies having a different decision-making process and level of interaction with the public, the application process is different. One application does not fit all. In some cases, there is an online application, while for others it is a lengthy written application with significant fees. The USDA prefers applications be submitted through the ePermits system (web-based application process).

Applying for field release with the USDA

If an organization is unsure whether their G.E. organism meets the definition of a regulated article as described in 7 CFR part 340, prior to proceeding with an application for a permit or notification, you may seek a confirmation of regulatory status of the G.E. organism

from USDA. The process for this is known as “Am I Regulated?” The “Am I regulated?” process is a letter or conversation with the Agency regarding the product and if it meets the criteria of being regulated or not. This is a conversation very early in the discovery phase of the project, so the organization can know how to proceed in compliance.

When a product is ready for field testing, the Applicant must apply to the USDA APHIS-BRS, the Agency uses the permitting process for products which it perceives as riskier while the notification process is used for biotech products which are less risky. For instance, an herbicide tolerant corn product would be under notification in most cases, while an herbicide tolerant wheat product would be under permit. The reason for the difference in the risk perception, may involve the fact that wheat is winter hardy, which means some types of wheat can persist over winter and pose a contamination risk. Each of these will then be reviewed by the Agency along with any supplemental documentation and how the biotech material will be managed or controlled while in handling, transit, storage, use/planting, in-season activities, harvest, and disposal of the material. The Agency’s intention is to control any unauthorized or accidental releases and the persistence of the regulated organism in the environment.

Biotech Regulatory Services (BRS) is a part of a science-based federal regulatory framework to protect the United States’ agricultural resources. BRS implements regulations on behalf of APHIS for some genetically modified organisms which may pose a risk to plant health. These are genetically modified plants which could outcross with other sexually compatible plants or the genetically modified organism could contain genetic material which originates from a virus or disease which originates from animals or humans, so it could pose a risk to their health.

A document called the design protocol is prepared by the Applicant to explain how the regulated biotech material will be managed. A Design protocol must be created for each crop planned for field testing. The Design Protocol provides details on all the activities involving the regulated material and how any risk will be managed. The Design Protocol must be submitted to the USDA and approved by them before any applications for regulated field release can be submitted or approved. The Design Protocol is the basis for compliance with the USDA. Applicants may be audited by the USDA and they will be audited against their own processes as outlined in the Design Protocol.

To develop a Design Protocol, there are a few options, the Applicant may take a previously approved Design Protocol and submit it to the Agency, so the Agency can suggest the changes needed, and the Applicant can determine if these are feasible or work for their business. If the changes are not significant, the applicant may just accept and incorporate them into the Design Protocol, so it can be submitted to the Agency for approval. There may be several back-and-forth exchanges between the Agency and Applicant. Another option would be for the Applicant to review all their conversations and interactions with the Agency through the year and try to make all the changes to the previous Design Protocol, then this could be submitted to the Agency for review, and again there would be several back and forth messages with the Agency to capture all their edits and approve the Design Protocol. The potential risk of this option, is that an organization may impose additional requirements on itself, for instance, an Auditor may make some suggestions at a site, so the Compliance Specialist may add this area of focus to the Design Protocol for the following year, yet the USDA wouldn't have added it to the Design Protocol, as the Agency didn't feel it was that high of a level of risk. A final possibility would be to start with a blank sheet and using the

template provided by the USDA's BQMS program. Again, the applicant would most likely still have several exchanges with the Agency to include all the adjustments needed. So, this process could take a few months, as the messages (emails) are exchanged with the Agency. It takes time for the Agency to review and suggest edits as it meets with its own experts and the applicant must weigh the changes to ensure they can be done and do not create additional risks. A separate Design Protocol is created for each crop and must be approved before any applications for release can be processed by the Agency.

To assist with the Design Protocol creation, the USDA created the Biotechnology Quality Management Support (BQMS) Program, a web-based module, which is flexible and customizable for Applicants. BQMS offers a series of modules to assist with compliance in a simple question and answer format. This is a voluntary system to provide support to Applicants in building their compliance structure. Some of the module topics include document control, record control, management review, training and critical control points, such as, storage, site selection, transport, and devitalization. This is an excerpt from the USDA BQMS storage module (2020):

1.0 **“PURPOSE:** This procedure describes the controls for storage of regulated genetically engineered (G.E.) organisms; the way in which the storage process is monitored; and whether the monitoring and verification, as well as any changes in those activities, are effective. For example, species of regulated G.E. organism addressed in this procedure is [species name].

2.0 **DEFINITIONS:** Insert any terms, acronyms or reference to a glossary here that may apply to this procedure. For the sake of clarity, indicate any deviations in your terminology from the definitions and terms used in 7 CFR part 340.

3.0 RESPONSIBILITIES

3.1 Identify and record the relevant personnel involved in the storage of G.E. organisms regulated under 7 CFR part 340. For example, this could be accomplished with an organizational charted or defined directly in the procedure. The level of specificity might identify any quality management representatives, corporate staff, field supervisors, or someone else engaged in the procedure to plan site selection. In some cases, this procedure might require your organization to obtain information from multiple departments according to your organization's structure (i.e.: legal, regulatory)-each of which could be described in this section.

4.0 STORAGE PROCEDURES

4.1 Describe how your organization's storage procedures keep regulated G.E. organisms will be segregated from other organisms. For example, procedures might describe marking or clearly labeling the containers and storing the containers in a separate location; this may be in the same store room. ...”

Each year a new Design Protocol must be approved by the USDA. There could be additional requirements based on past performance and additional risks found by the Agency. For example, if one of the locations used for release had multiple issues with bird feeding, the Agency might ask this to be addressed in the Design Protocol or the Agency could make a recommendation based on their audits of an organization, for instance if multiple sites had findings with their location signage or marking, then the Agency could ask the Applicant to address this, making changes to the process and clarifying it with their Growers during the season. The number of changes depends on updates to the Applicant's processes and additional risks from the Agency. Some examples of this risk would be differences in how

organizations are told to comply and thus what is included in the design protocol; the risk could also be through a large number of acres the Applicant has planned, as the more acres the Applicant has the more the potential of an error (the more times you do something the more likely something could go wrong). These errors or mistakes would reflect poorly on the Applicant and the USDA as the one over-seeing the process.

The planning process for regulated biotech trials is critical. During the application process, the Applicant must list the crop, phenotype conveyed and provide information on the transformation method and construct used in the transformation method (the transformation method is means by which the genetic makeup of the host plant is altered, which could be agrobacterium, the gene gun or other options) (the construct is the genetic material transferred to the host plant, the promoter, gene, terminator are examples of some of the parts of a construct). All the locations the regulated material may be physically moved to (shipped from an original location to various destinations) must be listed. Information on each release or planting location must be given to the Agency during the application process along with the name of the company conducting the work, a unique I.D. for the site, GPS coordinates, the name and contact information for the person conducting the trial, the acreage, and a short history of the planting area. The applicant should also assess the release locations for encroachment on critical habitat and proximity to Native American lands. By ensuring the release location doesn't infringe on critical habitat the applicant is protecting the environment and their own potential for negative feedback from the public. By assessing the proximity to Native American lands, the Applicant is ensuring they know the history and ownership of the land and have appropriate permissions for their study and that there is no potential for negative impact to the Native American Lands.

During the review and approval process of the application and Design Protocol the USDA may contact the Applicant to clarify or ask questions. The Agency may ask the Applicant to clarify the origin of one of the parts of the construct or to be more specific regarding the phenotype being conveyed in the application. For the Design Protocol the Agency may ask about part of the area planned for release due to concerns about a native plant that is sexually compatible or weedy relatives that are sexually compatible and how those will be addressed. This may require changes to the application or Design Protocol or an entirely new document to be submitted. The application process and subsequent reporting to the USDA are done through the ePermits system primarily, as it is the preferred method by the Agency; they will accept other options if the organization is small with limited resources for a time.

Purpose and Intent of a Compliance System Learning Module

One of the most critical structures in an organization is a compliance system. Compliance systems must be able to comply with government regulations which have an impact on an organization's right and ability to operate. Compliance is complicated and layered, as these layers include the regulations, the risk the organization is willing to take, and the capability of the organization. While this training focuses on biotech regulatory compliance, it can be applied to any organization that has rules to follow and it has the potential to be considered for other regulations (not just biotech) or information to be shared within an organization. It is important to have a specialized group that can interpret the regulations and coordinate with legal and the business groups to represent the organization and develop a communication plan for the learners or users. Along with this, the

communication plan for a compliance system needs to be flexible and can evolve with technological advancements, which impacts every level of the organization.

Initially, our learning plan was a manual and a long Power Point presentation, which was delivered in a phone conference with the learners. This model of learning had many limitations, including monitoring and assessment. Utilizing this old model, there was no way for trainers to determine if learners were listening let alone engaged in the content being disseminated in the training. As a result, this led to ineffective training where learners and users had a difficult time following the policies and procedures which were required by the company and the government. In cases like this, the compliance accountability and ownership reside with the instructor and compliance team rather than the user. This becomes problematic as noncompliance with policies have a detrimental impact on project timelines and in some cases, the project itself.

Through technological advancement and continuous policy enhancement, the manual material was updated each year; however, there are many challenges that come with creating a system of compliance that is understandable and useable by all the different groups in an organization. It is important to talk with the users to really develop a comprehensive system of compliance, but to do so, we must address the limitations of the older models. There are three aspects of training that must be addressed by the trainer:

1. What options do you have for the training?
2. What technology capability do your learners have to complete the training?
3. What do you really want the learner to leave the training knowing?

Initially our training was done by updating the manual, mailing it out, and then conducting a teleconference for the training. This delivery method was ineffective as many

learners were not actively participating in the training. Many learners were reading emails during the presentation and did not answer questions or ask any questions during the call. Due to these reasons, many learners did not fully understand the importance of compliance or the interpretation of the regulations and needed additional support on how to comply. This has led to more dire consequences such as a project not being able to continue or being halted.

To address the limitations of teleconference-based training, we developed a different model of training that was more flexible for our employees. This model was a power point-based presentation with a voice-over. Along with this model, employees could complete it on their own schedule, which allowed the learner to manage their time and retain the information from the training better. Once the training was completed, a learning assessment was the final step for certification of training. This learning assessment was crucial in determining how well the employees learned and could apply the information in the training.

Large agricultural corporations have the resources to develop various training options such as teleconference, face to face, video conference, and online learning. Many learners appreciate face to face training because of the hands-on interaction, while many instructors value the participation from the learners. The face-to-face training is difficult for many organizations due to cost and time. Now, we can offer the learner options on how to complete the compliance training, they can come on campus and have a face-to-face experience, they can complete the training online in our learning management system, or they can be trained by someone at their site that is a lead biotech contact. This allows the learner to select the training option that works best for them, while allowing the compliance team to reach a large audience. Once you evaluate the training options which are available

for use, it is important to think of which of those the learner can use. From our earlier training methods, everyone had a phone, but it was easy for them to be distracted by other tasks while listening; then when we were using a voice-over with a PowerPoint, the file type could be unplayable for some folks or the file was too large to send and be accepted by their organization through email. And even with face-to-face training there is the cost in both time and money by the company. So, it is important to weigh all these factors along with which method is the most effective in helping employees retain vital compliance information.

Finally, the goal of training for employees is to equip them with the vital compliance information they need to apply to their everyday activities. Based on this goal, the new training is streamlined and focuses on vital information such as shipping, inventory tracking, planting practices or isolation, and monitoring, and any audit findings from the USDA. In order to create an effective learning module to meet these goals, the manual was developed and made available to all learners to ensure they could find additional information and templates for required forms that must be completed.

Execution of New Training -Method

We implemented each of the components individually, the online training, in-person training and experts at the site teaching other people the compliance elements. This allowed us time to ensure each was in use and to gather feedback each year. We sent out a survey at the end of each year to see what we could improve. The first method we implemented was the online training due to the infrastructure we had to develop and communicate the training to the users. Then some of the functional groups in the organization reached out to us asking about in-person training, and if they were meeting at a site on or close to campus, that was how this originated, as we had not requested any additional travel budget. Asking learners to

come on campus originate from the end of year survey, though again, we needed a budget for the food and snacks, a large space, and some IT support for the day, in case of issues. We were able to make the business case for this expense based on the relationship and trust building along with the training. The last option to implement was for someone on the site that had successfully completed training to train others at their site, and this was due to the risk we, as the compliance team, imagined; our concerns stemmed from wanting to ensure the expert was high performing in relation to compliance and had the time to spend on the training. These three methods of training are the current options available for compliance training in the organization. And each of them is used, typically each year we have 30-60 people attend the training in person, and the number of people completing the training online is always high (as this can be increased by the external cooperators), and then the sites which employ the expert training method must provide documentation of this training during their internal audit.

Results

Due to the time, effort and emphasis the organization placed on compliance, 90-95% of the USDA inspections for the organization had no significant findings. This high level of compliance was a result of the employees' diligence and the compliance training. The results of the internal audits conducted as preparation for a USDA inspection, typically found minor documentation errors at the site, but no systemic compliance issues. The compliance experts at the site felt an additional level of responsibility for the compliance program. This led them to conduct additional training sessions and task-specific audits, which further boosted our compliance program.

Each year, we continue to refine the training and the techniques to deliver it. We update the training information based on feedback from the Agency, inspection and audit performance, and survey data from the users. As technology and learning software improves, so will the compliance training. We are implementing a new learning management software for use within the organization and have teams to review the training across the organization, so no one is doing training that doesn't apply to them anymore. The organization wants everyone to focus and go after their passion but be assigned training that doesn't add value to their performance.

Conclusion

The creation of multi-faceted training allowed the compliance team to disseminate compliance training and communication throughout the organization. We have implemented this training program with multiple options. All organizations have rules they have to follow, whether these are their own rules or rules imposed on them from other sources. So, having a group to take on that responsibility and communicate it to the required parts of the business is essential. If the rules aren't followed, the business won't be in business for long. This need for a compliance system and its goals can be applied to any organization, it just important to keep in mind how the training and communication will occur with the rest of the organization.

A compliance group allows the business to focus on product discovery and creation, rather than interpreting regulations or trying to determine which rules apply. This allows everyone in the organization to do what they are best at and were hired to do. Researchers don't want to focus on rules, they want to focus on their research, not break the rule, but focus on what matters most to them. We all want to focus on our job and do what we are

good at and hired to do. Researchers are hired for research not to do compliance. By allowing the organization to focus on their role and not supporting areas such as compliance, human resources, logistics, or research, the organization is able to flourish.

If you have a large infraction or enough small infractions, then the outside sources imposing rules could halt your business or impose fines on you. And in many cases the publicity of these infractions will also have a negative impact on the business. This can impact the ability of the business to have a right to operate. The organization leadership must support compliance and talk about it. Compliance isn't just the responsibility of the compliance team; it belongs to everyone. If the compliance program is strong and successful then the leadership and entire organization must talk about it and work together.

Since everyone in the company knew we were committed to compliance and heard its importance in multiple meetings, the importance of compliance went beyond what we alone could have done. We were able to see the value the manual and training brought through the learning assessments, visits to sites and feedback from the USDA. The learning assessments went well, but there was never a year that everyone got 100% the first time. During our visits most of the corrections we found revolved around internal documentation, all of the plots, shipments, and inventory were managed well, so we thought this was a good sign for our program. We also never had a lot of issue with our USDA audits, we had our fields marked and isolation in place, so much of the risk they were concerned about was addressed as we said we would per our Design protocols. During our site visits we would answer questions and help them prepare for an Agency audit, as best we could.

If our main goal was to keep the company out of news for any issues, then we did well, as we managed over 1,000 trials in the US per year which were regulated. We didn't

receive any fines or severe disciplinary letters. And all the researchers in the company knew they could call us anytime they had a question and we would do our best to answer them.

We also tried to help minimize any issues with their plots due to weather or animal damage and told them what we would do and what they needed to do. So, we were a calming force which was trusted by the business.

References

- Altpeter, F., N. Springer, L. Bartley, A. Blechl, T. Brutnell, V. Citovsky, et al. 2016. Advancing crop transformation in the era of genome editing. *The Plant Cell* 28(7):1510-1521.
- Bean, M. J. 2009. The endangered species act. *Annals of the New York Academy of Sciences* 1162(1):369-391. doi:10.1111/j.1749-6632.2009/04150/x
- Department of the Interior (2004). National environmental protection act revised Implementing procedures. *Fed.Regist.*69, 10866-10887.
- Economic Research Service. 2019. Recent trends in GE Adoption. Adoption of genetically Engineered crops in the United States, 1996-2019. USDA. <https://www.ers.usda.gov/Data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-Ge-adoption.aspx> (Accessed March 3, 2020).
- James, C. 2014. Global status of commercialized biotech/GM crops: 2014. International Service for the Acquisition of Agri-biotech Applications. Ithaca, NY.
- Krimsky, S., and R. P. Wrubel. 1996. *Agricultural biotechnology and the environment: Science, Policy, and Social Issues*. University of Illinois Press, Champaign, IL.
- NASEM. 2017. *Preparing for future products of biotechnology*. National Academies Press, Washington, DC.
- National Research Council [NRC]. 2013. *Assessing risks to endangered and threatened species from pesticides*. National Academies Press, Washington, DC.
- Office of Science, and Technology Policy [OSTP]. 1986. Coordinated framework for Regulation of biotechnology. *Fed. Regist.* 51, 23302-23350.
- Office of Science, and Technology Policy [OSTP] (1992). Exercise of federal oversight within scope of statutory authority: planned introductions of biotechnology products into the environment. *Fed. Regist.* 57, 6753-6762.
- Roh, J.Y., J.Y Choi, M.S. Li, B.R. Jin, and Y.H. Je. 2007. *Bacillus thuringiensis* as a Specific, safe, and effective tool for insect pest control. *Journal of Microbiology and Biotechnology*. 17(4):547-559.
- United States Code [USC]. 2012. Endangered species. <https://www.gpo.gov/fdsys/granule/USCODE-2011-title16/USCODE-2011-title16-chap35> (accessed 10 April 2020).
- FDA. 1992. Statement of policy: foods derived from new plant varieties. *Fed. Regist.* 57:22984.

- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statement-policy-foods-derived-new-plant-varieties> (accessed 10 April 2020).
- FDA. 2001. Premarket notice concerning bioengineered foods. Fed. Regist.66, 4706-4738.
- FDA. 2018. Biotechnology Guidance Documents and Regulatory Information. <https://www.fda.gov/food/guidanceregulation/Guidancedocumentsregulatoryinformation/biotechnology/default.htm>. (accessed 10 April 2020).
- USDA. 2016a. About the 2008 Proposed rule for APHIS Biotechnology Regulations. https://www.aphis.usda.gov/aphis/ourFocus/biotechnology/biotechnrulerevision/SA_08_Proposed_Rule (accessed 17 February 2018).
- USDA. 2016b. Environmental Impact Statement: Introduction to the products of Biotechnology. Fed Regist. 81, 6225-6229.
- USDA. 2017. Biotechnology quality management support (BQMS): Storage module. https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/bqms/bqms_user_orientation (accessed Mar 4, 2020).
- Wolt, J., and C. Wolf. 2018. Policy and governance perspectives for regulation of genome Edited crops in the united states. *Frontiers in Plant Science* 1606(9):1-12.