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"Introduction to Biotech: Environmental, Health & Safety Laws Commonly Affecting the Biotechnology Industry"

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INTRODUCTION

The term "biotechnology" encompasses a wide variety of products and techniques, and generally involves the use of various biological processes to make products and perform services from living organisms or their components.

"Biotechnology" has been around almost since the first time humans began domesticating plants and animals. People have used yeast, for example, to make unleavened bread, beer and alcohol for centuries. Farmers have been selectively breeding animals and "hybrid" crops for decades, and bacteria have long been used to modify food (e.g., creating cheese and yogurt from milk). Bacteria and other microorganisms have been used for years to "treat" environmental contamination in soil and groundwater, and other microbial processes have been employed in sanitary sewer systems. In short, selective breeding has long been used to enhance the natural characteristics of food, plants and animals.

However, "biotechnology" as many have come to know it now also includes newer technologies, such as recombinant DNA, recombinant RNA, and cell fusion. These forms of "genetic engineering" – i.e., placing foreign DNA into an organism - can create new life forms or alter an organism's original characteristics, sometimes with merely the insertion of a single gene. Food crops can be genetically modified to tolerate herbicides or resist infection. Genetic engineering has resulted in edible vaccines and anti-coagulant compounds, the enhancement of vitamins and minerals, and the production of numerous anti-cancer and cholesterol-fighting substances. These technologies provide endless possibilities for reducing pollution, increasing agricultural productivity, and fighting disease.

The possibility of creating new treatments for disease and environmental contamination, safer food products and less damaging chemicals has spurred incredible growth in the field of biotechnology. In North Carolina alone, biotechnology and related bioscience technologies are projected to generate up to $15 billion in annual product sales and employ as many as 100,000 people within the next 15 years. Biotech, and related "life sciences" technologies, are anticipated to continue representing one of the fastest growth industries in the United States.

FEDERAL REGULATION OF BIOTECHNOLOGY

Until relatively recently, no special statutes were found to be necessary to oversee and regulate the production of genetically engineered organisms, and existing legal frameworks were deemed to be adequate. The first major consideration of the need to supervise this field under a unified regulatory framework came in 1986, when the President's Office of Science and Technology Policy ("OSTP") published its "Coordinated Framework for Regulation of Biotechnology." Generally speaking, the Framework concluded that existing regulatory schemes - under the auspices of several different federal agencies - provided adequate regulatory supervision and safeguards over this field. The Framework provided a broad product-specific and multi-agency approach to regulating the entry of biotechnology products into commerce.[1] Rather than seek new legislative authority, the OSTP concluded that existing laws, supplemented by new regulations tailored to biotechnology issues, could effectively regulate

[1] "Coordinated Framework for Regulation of Biotechnology: Announcement of Policy and Notice for Public Comment," 51 Federal Register 23302 (June 26, 1986).

biotechnology products. The Framework has been reaffirmed throughout subsequent Administrations through the Clinton Administration. [2]

However, the Framework's conclusions were premised on significant coordination among different federal agencies, and did not address how regulatory authority should be exercised in situations where the statute leaves the implementing agency latitude for discretion. The OSTP attempted in 1992 to address these issues in its second policy statement, which generally concluded that actual risk to the public health and the environment - and not merely "the fact that an organism has been modified by a particular process or technique" - should be dispositive on the issue of regulatory discretion.

As noted above, the OSTP's conclusions to date - and the continued lack of a single, unified regulatory framework for "policing" the field of biotechnology - are based largely on the supposed adequacy of other environmental, health and safety regulatory schemes and the administrative powers wielded by several federal agencies. In fact, the extreme diversity of biotechnology-generated applications (e.g., in the fields of agriculture, medicine, pharmaceuticals, and environmental protection), combined with the myriad substances and processes utilized in connection with these technologies, generally result in regulation under more than one regulatory regime. There are three federal agencies that are primarily in charge of regulating biotechnology companies in the United States: the Environmental Protection Agency ("EPA"), the Food and Drug Administration ("FDA"), and the Department of Agriculture ("USDA"). For the most part, agency regulation of biotechnology products is dependent upon the intended use of a given product. Some of the more common laws and programs administered by these agencies are discussed briefly below.

[2] Testimony of Janet L. Anderson, Ph.D., Director, EPA's Biopesticides and Pollution Prevention Division, before the U.S. House of Representatives' Committee on Science Subcommittee on Basic Research, October 19, 1999.

EPA Regulation of Biotechnology Products

1. Environmental Protection Agency

The EPA is generally responsible for protecting the environment and safeguarding human health. In this role, the EPA is charged with regulating hundreds of substances and materials that could adversely affect the environment. The primary laws used by the EPA to regulate the field of biotechnology are the Toxic Substances Control Act ("TSCA") and the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). Although it is not widely known, the EPA also administers certain portions of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), particularly as amended by the Food Quality Protection Act ("FQPA"). EPA's role in biotechnology regulation generally focuses on whether a biotechnology product could adversely affect human health or the environment. EPA regulates numerous biotechnology products, such as intergeneric microorganisms used for commercial purposes, bioengineered pesticides, and bioengineered plants with pesticidal characteristics. EPA regulates genetically engineered non-pesticidal microorganism products under TSCA, and pesticidal products and their residues under FIFRA and the FFDCA, respectively, including genetically engineered microorganisms and plant-pesticide products. As a product safety law, TSCA is similar to FIFRA in that it requires submission of large quantities of technical data to EPA; however, TSCA neither requires affirmative agency approval before marketing (as does the FFDCA), nor a licensing process (as does FIFRA).

I. TSCA

A. Introduction to TSCA

Enacted in 1976, TSCA's goal is to "prevent unreasonable risks of injury to health or the environment associated with the manufacture, processing, distribution in commerce, use or disposal of chemical substances." Unlike most environmental laws that control product use or waste disposal activities, TSCA regulation occurs much earlier at the pre-manufacturing stage before chemicals are introduced into the stream of commerce. Although TSCA imposes most of its requirements on a chemical substance manufacturer, it also applies to any person who processes, distributes in commerce, uses, or disposes of a chemical substance.

B. Scope of TSCA Includes "Intergeneric Microorganisms"

TSCA's broad scope and application is tied to the definition of "chemical substance,"[3] a term that includes all new and existing chemical substances manufactured, imported, processed, used, distributed, or disposed of in the United States. EPA interprets TSCA's definition of "chemical substance" to include "intergeneric microorganisms" (microorganisms formed by combining genetic material from organisms in different genera). For purposes of TSCA jurisdiction, EPA specifically

[3] The term "chemical substance" is defined as "any organic or inorganic substance of a particular molecular identity, including – (i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature and (ii) any element or uncombined radical." 15 U.S.C. § 2602(2)(A).

defines the term "intergeneric microorganism" as a microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.

EPA considers intergeneric microorganisms analogous to new chemicals because they have a sufficiently high likelihood of expressing new traits or new combinations of traits. As such, EPA believes that the introduction and use of intergeneric microorganisms in commerce must be subject to governmental scrutiny to determine whether they present an unreasonable risk to human health or the environment. A "new intergeneric microorganism," like a "new chemical substance" is one that is not listed on the TSCA Chemical Substances Inventory.[4] Microorganisms that are not intergeneric are not considered "new", and thus would not be subject to TSCA. Examples of biotechnology products that would not be considered "new" include industrial enzymes, biofertilizers, and compounds developed to treat environmental contamination.

TSCA jurisdiction does not cover substances that fall under the jurisdiction of FIFRA and the FFDCA. As such, TSCA does not cover microorganisms used as pesticides, foods, food additives, drugs, cosmetics, and medical devices. Consequently, if research is conducted with the intention of developing a product, the use of which would be subject solely to the FFDCA, the research would not be subject to TSCA. Microorganisms manufactured or imported for both a TSCA and non-TSCA use, however, are subject to both applicable statutes.

C. Key TSCA Reporting Requirements for Biotechnology Companies

In 1997, EPA adopted regulations tailoring TSCA's Section 5 screening and reporting requirements for new chemical substances to biotechnology products.[5] Theses regulations establish a formal process for screening intergeneric microorganisms and establishing procedures for EPA's review of new genetically engineered intergeneric microorganisms. EPA's 1997 regulations for new biotechnology products incorporate many of the procedures originally developed for the TSCA Section 5 program for traditional chemicals, albeit with modifications necessary to accommodate the specific characteristics of these microorganisms.

TSCA's principal reporting requirements for manufacturers and processors of intergeneric microorganisms include the following:

1. Microbial Commercial Activity Notice.

[4] 40 C.F.R. § 725.3. Section 8(b) of TSCA requires EPA to establish an inventory of all chemical substances manufactured or processed in the United States. 15 U.S.C. § 2607(b). Initially published in 1979, the TSCA Chemical Substances Inventory establishes the baseline list of existing chemical substances. All chemical substances that do not appear on the Inventory are, by definition, "new chemical substances" subject to TSCA's review and approval process.

[5] The 1997 biotechnology regulations, codified in 40 C.F.R. Part 275, supersede (but substantially follow) prior EPA policy documents issued in 1986. The regulations continue EPA's focus on new intergeneric microorganisms that are likely to display new traits or exhibit less predictable behavior in the environment.

The 1997 regulations created a reporting vehicle specifically designed for living microorganisms, the Microbial Commercial Activity Notice ("MCAN"). Like TSCA's premanufacture notification ("PMN") process for traditional chemical substances[6], the MCAN process is designed to evaluate the risks of new intergeneric microorganisms prior to their entry into commerce. Subject to certain exemptions, any person who manufactures, processes, or imports a new intergeneric microorganism must submit a MCAN to EPA at least 90 days before commencement of manufacture, processing, or import of an intergeneric microorganism that is not listed on the TSCA Inventory. In addition, any person who desires to manufacture, process, or import an existing intergeneric microorganism for a significant new use must submit a MCAN at least 90 days before manufacturing, processing, or importing a microorganism for a significant new use.

TSCA Section 5 reporting only applies to microorganisms that are manufactured, imported, or processed for commercial purposes. EPA defines the phrase "manufacture, import, or process for commercial purposes" as "manufacture or process for purposes of obtaining an immediate or eventual commercial advantage." EPA suggests that whether an activity has an immediate or eventual commercial advantage is determined by indicia of commercial intent.

Certain research and development activities may require filing a MCAN. EPA considers research and development activities are for commercial purposes, and thus subject to reporting, "if tests are directly funded, in whole or in part, by a commercial entity; or if the research and development activities are not directly funded by a commercial entity, if the researcher intends to obtain an immediate or eventual commercial advantage." In addition, all post-research and development activities are considered manufacturing or processing for a commercial purpose.

To the extent it is known or reasonably ascertainable, a person submitting a MCAN must include the following information relating to the manufacture, processing, distribution in commerce, use and disposal of the new microorganism: name and address of the submitter; identity of the microorganism; description of byproducts resulting from the manufacture, processing, use, and disposal of the new microorganism; estimated maximum amount of the new microorganism intended to be manufactured or imported; description of uses by function and application; information on worker exposure and on release of the microorganism to the environment; and a $2,500.00 fee for each MCAN submitted.

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[6] 15 U.S.C. § 2604; 62 Federal Register 17910-17958 (April 11, 1997). Section 5 of TSCA generally requires that manufacturers of a "new chemical substance" or the manufacture or processing of an existing chemical substance for a "significant new use" submit to EPA a pre-manufacturing notice ("PMN") or significant new use notice ("SNUN") at least 90 days before manufacture or use commences. EPA then has 90 days to respond, absent which the substance may be manufactured, sold, used, and disposed of throughout the United States. The process requires an applicant to provide EPA with detailed information relating to the new chemical's structure, production quantity, proposed use, and environmental and health effects. Section 5 of TSCA also authorizes several exemptions from the PMN requirements, such as exemptions for research and development, test marketing, chemicals produced solely for export, and chemical substances that EPA already has determined do not present an unreasonable risk to health or the environment.

TSCA only requires that the MCAN be accompanied by existing health and environmental studies on a new microorganism, which is in the possession or control of the submitter. TSCA does not require that a submitter generate new studies for a MCAN submission.

The MCAN review period runs for 90 days after EPA's receipt of a complete MCAN. EPA may extend the review period for an additional 90 days. During the 90-day review period, EPA determines whether the planned use of the new intergeneric microorganism presents an unreasonable risk to public health or the environment and whether the new intergeneric organism (or significant new use of an existing intergeneric organism) warrants further testing, limitations, or other necessary actions.

EPA may list the microorganism on the TSCA Inventory upon receipt of an adequate and complete MCAN, expiration of the MCAN review period, and EPA's receipt of a notice of commencement ("NOC") of manufacture or import from the submitter.[7] Alternatively, if EPA determines that the microorganism may present an unreasonable risk, or if the substance may be expected to enter the environment in substantial quantities, but there is insufficient information to adequately evaluate the chemical, EPA may require testing of the microorganism. EPA may restrict or ban the manufacture, processing, or distribution in commerce of new intergeneric microorganisms and/or designated significant new uses of intergeneric microorganisms.

2. MCAN Exemptions and Alternative Reporting Mechanisms

Most exemptions to full MCAN reporting create an alternative mechanism for reporting to EPA that reduces the amount of information that must be reported.

a. General Exemption – No Unreasonable Risk. A general exemption from MCAN requirements exists for microorganisms that EPA can determine will not present an unreasonable risk to health or the environment, based upon a balancing of the magnitude and severity of the harm to health or the environment a microorganism may cause, with the social and economical effects on society of EPA action to reduce the harm.

b. Tier I and Tier II Exemptions. EPA also has established two specific exemptions for new microorganisms that meet certain criteria. These exemptions are known as the Tier I and Tier II exemptions for fermentation applications.

c. Research and Development Exemptions. If a manufacturer is conducting research and development activities solely within a "contained structure," the research may qualify for an exemption.[8]

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[7] The NOC must be filed with EPA no later than 30 calendar days after the first day of such manufacture or import and contain the following information: specific microorganism identity, MCAN number, and the date when manufacture or import commences. 40 C.F.R. § 725.190.

[8] For traditional chemical substances, a research and development exemption exists for chemical substances manufactured or imported only in "small quantities" that are not greater than reasonably necessary for research and development purposes. 15 U.S.C. § 2604(h)(3). EPA did not extend a similar "small quantity" exemption to microorganisms because unlike traditional chemical substances, "living organisms may reproduce and increase

A manufacturer or importer may opt to submit a TSCA Experimental Release Application ("TERA") for new intergeneric microorganisms that are to be used commercially in the United States for research and development purposes. The TERA process only applies to research and development activities that cannot qualify for the contained structure exemption and are not otherwise exempt from MCAN requirements. A TERA is an abbreviated MCAN submission for individual tests. To the extent known or reasonably ascertainable by the submitter, a TERA application must include detailed information on the proposed research and development activity, and information on monitoring, confinement, mitigation, and emergency termination procedures. As with the MCAN, a manufacturer also must include health and safety data regarding the new microorganism that are within the possession or control of the manufacturer.

A TERA must be filed with EPA at least 60 days prior to field testing. EPA's review period is reduced to 60 days, although EPA may extend its review for good cause. EPA must approve the test before the researcher may proceed, even if the 60-day review period expires. EPA's approval is limited to the conditions outlined in the TERA notice or approval. Like the MCAN process, to gain approval for the TERA, EPA must determine that the proposed research and development activity for the new microorganism does not "present an unreasonable risk of injury to health or the environment."

Although a manufacturer may submit a MCAN for any research and development activity, it is anticipated that most will choose to submit a TERA to allow researchers greater flexibility and shorter review periods. In addition to the longer review period under the MCAN process, EPA anticipates that because of the limited information available at the research and development stage, EPA most likely would issue a TSCA Section 5(e) order imposing conditions to address uncertainties that would need to be modified each time the manufacturer desired to vary the terms of the order.

d. Test Marketing Exemption. Test marketing activities usually involve limited sale or distribution of a substance within a predetermined period of time to determine its competitive value when its market is uncertain. Although EPA suggests that manufacturers who intend to test market a new microorganism file a MCAN, a manufacturer may submit an application for a test marketing exemption ("TME"). A TME application is most appropriate for microorganisms that EPA previously reviewed at the research and development stage. A TME application must include information concerning the microorganism's identity, phenotypic and ecological characteristics, maximum quantity of the microorganism and duration and route of exposure of persons to the microorganism, and all existing health and environmental effects data. EPA must approve or deny the application within 45 days after its receipt. A submitter only may proceed with test marketing activities after receipt of EPA approval.

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beyond the number initially introduced, may establish in the environment, and may spread beyond the test site [and] once they are released into the environment or are no longer contained, there is no longer an assurance they will remain 'small quantities.'" 62 Federal Register at 17,923. Therefore, the research and development exemption for microorganisms requires that the research and development activities be conducted within a contained structure designed to reduce the probability of establishment by reducing the number and frequency of viable microorganisms emitted from a facility. *Id*.; 42 C.F.R. §§ 725.234, 725.235.

D. Confidentiality of TSCA Submissions.

Since much of the data required for a TSCA Section 5 filing may include commercially sensitive information, regulated biotechnology companies may have a significant interest in assuring that such information remains confidential to the extent allowed by law. Subject to certain limited exceptions, EPA is prohibited from disclosing to the public trade secrets and commercial or financial information that is privileged or confidential.

A claim of confidentiality, with substantiating documentation, may be asserted in connection with a MCAN, TME, or Tier I/II exemption request on the grounds that the information constitutes a trade secret or confidential business information ("CBI"). Upfront substantiation is not required for a confidentiality claim in connection with a TERA.

All CBI claims must be asserted at the time the information is submitted to EPA. Each time information is filed with EPA, a confidentiality claim must be reasserted and substantiated. If the information is not claimed confidential when filed, EPA may disclose the information to the public without further notice to the submitter.

E. Enforcement

Violations of TSCA's biotechnology regulations, including any failure to submit any required report, notice, or other information are subject to EPA enforcement action, including the assessment of civil penalties up to $25,000 for each day of violation. Knowing or willful violations can result in additional penalties of up to $25,000 per day per violation and imprisonment up to one year. Like most environmental statutes, TSCA is a strict liability statute. Thus, there is no requirement that a violator's conduct be knowing or willful before civil penalties may be imposed. At least one commentator has noted that EPA has a "well-established history" of bringing administrative enforcement actions and seeking large penalties against chemical manufacturers, importers, and processors subject to TSCA regulation.

II. FIFRA AND SECTION 408 OF THE FFDCA

EPA regulates genetically engineered non-pesticidal microorganism products under TSCA. FIFRA and Section 408 of the FFDCA bridge the TSCA regulatory gap regarding pesticides, including pesticides developed through biotechnology. FIFRA is designed to prevent adverse health and environmental effects from pesticide usage primarily through registration, labeling and other regulatory requirements. Section 408 of the FFDCA establishes the maximum legally permissible levels of pesticide residues in food. Although the EPA sets the safe tolerance level, and may revoke or change the safe tolerance level as the facts warrant, the FDA is responsible for their enforcement. EPA generally administers those portions of the FFDCA relating to microbial/plant pesticides and novel organisms, while the FDA focuses more on the provisions relating to food, feed, drugs, and medical devices.

The following is a brief summary of each law and EPA's regulatory role, focusing upon key

requirements that are potentially applicable to non-traditional pesticide products developed through biotechnology.

A. Introduction to FIFRA

Subject to certain exemptions discussed more fully below, FIFRA requires any "pesticide"[9] to be registered with EPA prior to being sold, distributed, or used in the United States. As a licensing and registration statute, FIFRA provides pre-market clearance of pesticide products and post-market surveillance of pesticides to ensure that they do not cause unreasonable adverse effects to human health and the environment. EPA's regulations implementing FIFRA are codified at 40 C.F.R. Parts 150-189.

Since FIFRA's enactment in 1947, pesticide products developed by biotechnology companies, such as crops that are bred or genetically modified to resist pests, have become increasingly important to agricultural production. Until recently, EPA chose to regulate these newer, emerging biotechnology products by applying, in some cases, old procedures and programs developed for traditional chemical pesticide products. In 2001, EPA finally adopted new FIFRA regulations to specifically address genetically engineered microorganisms that are intended to be used as pesticides.

B. Traditional Chemical Pesticide Regulation under FIFRA

1. *Intended Use is Determinative*

Under EPA's traditional framework for regulating pesticides, a substance's intended use determines whether a product is a pesticide.[10] A substance is considered to be a pesticide requiring registration if:

> (a) the person who distributes or sells the substance claims, states or implies (by labeling or otherwise) that (i) the substance (either by itself or in combination with other substances) can or should be used as a pesticide, or (ii) the substance consists of or

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[9] FIFRA defines the term "pesticide" as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest," and "any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant." 7 U.S.C. 136(u). A "pesticide" does not include any article that is a new animal drug or a new animal feed regulated by FDA. *Id*. EPA's regulations further define the term as "any substance or mixture of substances intended for a pesticidal purpose (*i.e.*, used for the purpose of preventing, destroying, repelling or mitigating any pest)." 40 C.F.R. § 152.15. The term "pest" is defined as "any insect, rodent, nematode, fungus, weed, or … any other form of terrestrial or aquatic plant or animal life or virus, bacteria or other microorganism (except viruses, bacteria, or other microorganisms on or in living man or other living animals)." 7 U.S.C. § 136(t).

[10] In a 1981 proposed rulemaking, EPA stated:

> When a living organism is intended for use as a biological control agent to prevent, repel, destroy or mitigate a pest, or is intended for use as a plant growth regulator, defoliant, or desiccant, it is considered to be a pesticide under FIFRA, section 2(u), and is therefore regulated under the Act.

46 Federal Register 18,322 (1981).

contains an active ingredient and that it can be used to manufacture a pesticide;

(b) the substance consists of or contains one or more active ingredients and has no significant commercially viable use as distributed or sold other than (i) use for pesticidal purpose (by itself or in combination with any other substance), or (ii) use for manufacture of a pesticide; or

(c) the person who distributes or sells the substance has actual or constructive knowledge that the substance will be used, or is intended to be used, for a pesticidal purpose.

Pesticides are regulated primarily on the basis of their "active ingredients"—the ingredient that gives a product its pesticidal effect. The term pesticide may refer to an active ingredient used in the formulation of other products or a formulation that combines one or more active ingredients with one or more inert ingredients.[11] Administrative burdens and data requirements are considerably reduced if the source of the active ingredient is already registered.

2. Exemptions EPA may exempt any pesticide from FIFRA if EPA determines either (1) that the pesticide is "adequately regulated by another federal agency, or (2) that the pesticide is "of a character" making FIFRA requirements unnecessary (*i.e.*, does not pose an unreasonable adverse risk to human health or the environment).

EPA has determined that the following pesticides (or classes of pesticide) are exempt from FIFRA requirements because they are adequately regulated by another federal agency:

(a) Certain biological control agents[12], except (i) eucryotic microorganisms (including protozoa, algae and fungi), (ii) prokaryotic microorganisms (including bacteria), and (iii) viruses.

(b) All living plants intended for use as biological control agents (except PIPs as discussed below); and

(c) A pesticide product that is offered solely for human use and is regulated as a new drug under the FFDCA.

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[11] According to EPA, there are over 865 active ingredients registered as pesticides, which are formulated into thousands of pesticide products that are available in the marketplace. "Assessing Health Risks from Pesticides," EPA Office of Pesticide Programs, January, 1999.

[12] "Biological control agent" means any living organism applied to or introduced into the environment that is intended to function as a pesticide against another organism declared to be a pest by the [EPA] Administrator." 40 C.F.R. § 152.3. The exemption for biological control agents does not apply to microorganisms since the listed exception essentially covers the entire field of microorganisms. Instead, this exemption covers maccroorganisms used as biological control agents because EPA believes that macroorganisms are adequately addressed by the USDA and the Department of Interior. Anderson, William L., *et al*., Biotechnology Deskbook, p. 35, n.26, *citing* Statement of Policy, Plant Pesticides Subject to FIFRA and FFDCA, 59 Federal Register 60,496 (November 23, 1994).

Exemptions for pesticides, which have been determined by EPA to be of a character not requiring FIFRA regulation, include, but are not limited to, the following:

- treated articles or substances (*e.g.*, paint treated with a pesticide to protect the paint coating, or wood products treated to protect the wood against insect or fungus infestation), provided the pesticide is registered for such use;

- preservatives for biological specimens;

- products consisting of foods and containing no active ingredients which are used to attract pests; and

- products qualifying as minimum risk pesticides in accordance with EPA regulations.

C. Registering Conventional Pesticide with EPA

A pesticide may be registered for general use, restricted use, or a combination of general and restricted use. If EPA determines that a pesticide, when applied in accordance with its directions for use or in accordance with widespread commercially recognized practice, will not generally cause unreasonable adverse effects on the environment, then EPA will classify the pesticide (or its particular uses) for general use. If EPA determines, however, that a pesticide, when applied in accordance with its directions for use or in accordance with widespread commercially recognized practice may cause, without additional regulatory restrictions, unreasonable adverse effects on the environment (including injury to the applicator), then EPA will classify the pesticide (or its particular uses) for restricted use. Restricted use pesticides that are determined to cause acute dermal or inhalation toxicity hazardous to the applicator or other persons must be conducted by a certified applicator. EPA also may establish other restrictions on any restricted use pesticide whose application is determined to result in unreasonable adverse effects on the environment.

To register a new pesticide with EPA, an application generally must contain test data showing that the pesticide will perform its intended function without unreasonable adverse effects on the environment and human health.[13] EPA requires a wide range of data in support of the application that varies depending on the composition of the pesticide and its intended use. Generally, EPA requires data concerning product chemistry, environmental and mammalian toxicity, environmental fate, residue

[13] Although this manuscript focuses upon the unconditional registration process for a new pesticide, there are other types of pesticide registrations authorized by FIFRA, including conditional registrations (where the applicant must submit within a specified time additional data supporting the registration), sub-registrations (where one person distributes a pesticide as the agent of another person), state special needs registrations (where sale and distribution of a pesticide is sought within a state for specific uses only), restricted use registrations (where the subject pesticide can only be applied by certified applicators), and emergency exemption registrations (where use of a federally registered pesticide is sought for an additional crop or to control additional pests in emergency situations). 7 U.S.C. §§ 136a(c)(7), 136a(d), 136v(a)-(c), 136p; 40 C.F.R. § 152.32.

chemistry, reentry exposure, and spray drift.[14] Pesticide registration studies must be conducted in compliance with "good laboratory practice requirements" and testing facilities conducting supporting studies are subject to EPA compliance inspections to assure the quality and integrity of all data submitted during the registration process. Registrations are transferable without submittal of a new application, provided a transfer application (in form approved by EPA) is submitted for EPA's approval and signed by both the transferor and transferee.

Although each applicant must submit its own data in response to data requirements that are specific to individual products, alternative data sources may be utilized for data requirements pertaining to the pesticide's "active ingredient." In response to "active ingredient" data requirements, an applicant may submit original data, cite publicly available data, or cite data submitted to EPA by another applicant, subject to the following limitations:

> FIFRA gives an "original data submitter" a ten-year period of exclusive use of data submitted to support initial registration of a pesticide or to register a new use of a previously registered pesticide. During that time, no other applicant for registration can rely on the data unless the data owner consents. Following the period of exclusive use and for all other data, an applicant can rely on data submitted by another party if it offers to compensate the data owner for their use.[15]

Under what is commonly referred to as the "formulator exemption," an applicant who purchases a registered pesticide from another producer in order to formulate it into the applicant's product does not have to submit or cite to data pertaining to the active ingredient in a formulated product or offer to pay compensation for such data. EPA has interpreted the "formulator exemption" to extend only to uses listed on the manufacturing use product label.

To facilitate the application review process, EPA's Office of Pesticide Programs, Registration Division, is organized into product teams, by type of pesticide, to review pesticide applications. EPA's review of a pesticide registration involves a balancing of risks posed by use of the pesticide with the benefits associated with its use. Specifically, EPA must register and approve a pesticide if it determines, after consideration of any restrictions that may be placed on the pesticide's use, the following:

(a) the pesticide's composition is such as to warrant the proposed claims for it;

(b) its labeling and other materials required to be submitted comply with [FIFRA];

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[14] EPA has adopted elaborate tables setting forth the information and data necessary for particular uses and types of pesticide products. *See*, 40 C.F.R. Part 158. Data requirements for approval of a microbial pesticide are specifically set forth in 40 C.F.R. § 158.740. EPA also has established Pesticide Assessment Guidelines that list "the standards for conducting acceptable tests, guidance on evaluation and reporting of data, definition of terms, further guidance on when data are required, and examples of acceptable protocols." 40 C.F.R. § 158.08.

[15] Bergeson, Lynn L., Federal Insecticide, Fungicide, and Rodenticide Act, p. 115 (2000).

(c) the pesticide will perform its intended function without unreasonable adverse effects on the environment;[16] and

(d) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

D. FIFRA Experimental Use Permits

Persons preparing a pesticide registration application (or application for approval of an additional use of a registered pesticide) often want to conduct testing to accumulate additional information in support of a FIFRA application. An experimental use permit ("EUP") is generally required for testing of any unregistered pesticide or any registered pesticide being tested for an unregistered use. An EUP allows use of a pesticide for experimental or research purposes only in accordance with the limitations in the permit. EPA must render a decision on the experimental use permit application within 120 days after receipt of a complete application. Permits usually are effective for one year.

An EUP is not required when experimental use of the pesticide is limited to laboratory or greenhouse tests, limited replicated field trials, or other field tests where the purpose is to determine whether the substance has value as a pesticide or to determine its toxicity, as long as the producer and applicator do not receive any pest control benefit and the test is conducted on less than 10 acres of land or a surface acre of water. If the pesticide will be used in a way that may result in residues in or on food or feed, the EUP applicant must (i) show that an appropriate tolerance level (or exemption from the tolerance requirement) has been established under Section 408 of the FFDCA, (ii) submit a petition proposing that a new tolerance level or tolerance exemption be established, or (iii) certify that the food or feed derived from the experimental program will be destroyed or fed only to experimental animals for testing purposes, or otherwise properly disposed.

E. Confidentiality.

Under FIFRA, data filed with EPA in support of a pesticide registration application remains confidential and not subject to public disclosure until 30 days after a registration is issued. After issuance of a pesticide registration, only trade secrets and CBI, subject to certain exceptions, may be protected against public disclosure. Upon determining that such disclosure is necessary to protect against an unreasonable risk of injury to human health or the environment, EPA may disclose trade secret and CBI under certain circumstances.

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[16] The phrase "unreasonable adverse effects on the environment" means both "(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food" inconsistent with the standard under section 408 of the FFDCA. 7 U.S.C. 136(bb). This latter criteria regarding human health risks posed by residues in food arises under the Food Quality Protection Act, which broadened FIFRA's scope to include pesticides that may result in residues in or on food.

III. INTRODUCTION TO THE FFDCA

The EPA and the FDA share responsibility for administering the FFDCA. As noted earlier, the portions of the FFDCA administered by the EPA generally are those that relate to microbial/plant pesticides and novel organisms, while the FDA focuses more on food, feed, drugs and medical devices. Due in part to the inconsistencies between the FIFRA and FFDCA over pesticide regulation, in 1996 the United States Congress passed the FQPA, which amended both FIFRA and FFDCA. EPA also regulates pesticides under Section 408 of the FFDCA. The FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that is "adulterated." Food is deemed adulterated if, among other things, "it bears or contains a pesticide chemical residue that is unsafe" within the meaning of Section 408 of the FFDCA. Under Section 408(a)(1) of FFDCA, any pesticide residue in or on a food shall be deemed unsafe unless a tolerance is in effect and residues are within the tolerance.

The FQPA, which amended both the FIFRA and the FFDCA in 1996, authorizes EPA to set tolerances, or maximum legal limits, for pesticide residues in food or animal feed.[17] The 1996 FQPA also established a single, health-based standard for setting pesticide residue tolerances in all types of food. This single standard eliminated the long-standing problems posed by different standards for pesticides in raw agricultural commodities[18] ("RAC") and processed foods. A separate tolerance (or exemption from a tolerance) for processed food is not necessary if residues in the processed food do not exceed the tolerance for the corresponding RAC. If the residues in the processed food exceed the corresponding RAC tolerance, then EPA must establish a separate tolerance under Section 408 for the processed food.

The tougher safety standard prescribed by the FQPA is defined as that level at which there is "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." The new safety standard is measured considering the aggregate risk from dietary exposure and other non-occupational sources of exposure, such as drinking water and residential lawn uses. In addition, when setting new, or reassessing existing, tolerances under the new standard, the EPA must now focus explicitly on exposures and risks to infants and children.

The FQPA also provides for expedited approval of safer pesticides and creates incentives for the development of effective crop protection tools for American farmers.

A pesticide that is used on, in or near growing crops, livestock, or food may require a tolerance or tolerance exemption, even if the pesticide is exempt from FIFRA requirements under FIFRA § 25(b) (*i.e.*, minimum risk pesticides). EPA will not register the use of a pesticide in connection with food or

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[17] The EPA maintains a database of pesticide residue tolerances on the Internet at http://www.epa.gov/opprd001/tolerance/tisinfo/.

[18] "Raw agricultural commodity" means any food in its raw or natural state, including all unprocessed fruits, vegetables, nuts, and grains." Foods that have been washed, colored, waxed, or otherwise treated in their unpeeled natural form are considered to be unprocessed.

animal feed unless (1) EPA has established the needed tolerance and when the pesticide is used as directed, any residue falls within the tolerance, (2) EPA has established a tolerance exemption, or (3) the pesticide is "genetically recognized as safe" ("GRAS"). If it is not possible to establish a needed tolerance or tolerance exemption for pesticide residues, EPA will not register the pesticide for the use that would result in such residues.

RACs and processed foods are illegal and cannot be sold or distributed if they contain pesticide residues not authorized by, or in excess of, applicable tolerance levels prescribed by EPA.

IV. FIFRA AND FFDCA REGULATION OF BIOTECHNOLOGY-DERIVED PESTICIDE PRODUCTS

A. Initial Biopesticide Regulation.

Since the 1980's, EPA has taken the position that any substance produced in plants that enables the plant to resist pests or diseases constitutes a "pesticide", and thus, is regulated under both FIFRA and the FFDCA. In 1994, EPA formed the Biopesticides and Pollution Prevention Division to facilitate registration of "biopesticides" which are made from natural materials (*i.e.*, plants, animals, minerals, and microorganisms unlike conventional chemical pesticides). EPA views biopesticides as generally posing less risk than conventional chemical pesticides because they are inherently less harmful than chemical substances, generally affect only the target pest and closely related organisms, and often are effective in very small quantities and decompose quickly, thereby resulting in lower exposure and pollution problems. For these reasons, EPA generally requires less data to register a biopesticide than to register a chemical pesticide. New biopesticides often are registered in less than one year, compared with an average of 3 years for conventional pesticides. By the end of 1998, EPA had registered approximately 175 biopesticide active ingredients and 700 products.

Biopesticides fall into three major classes:

(1) Microbial Pesticides. Microbial pesticides consist of a microorganism (*e.g.*, bacterium, fungus, virus, or protozoan) as the active ingredient. The most widely used microbial pesticide is *Bacillus thuringiensis* or "Bt" which produces a protein that kills certain insect larvae.

(2) Biochemical Pesticides. Biochemical pesticides are naturally occurring substances that control pests by non-toxic mechanisms, such as insect sex pheromones that interfere with mating and various scented plant extracts that attract pests to traps.

(3) Plant-Pesticides. Plant-pesticides are pesticidal substances that plants produce from genetic material that has been added to the plant. EPA regulates both the pesticidal substance and its genetic material. Although EPA does not regulate the plant itself, the USDA may regulate plants used as biological control agents.

In November 1994, EPA proposed regulations describing EPA's policies for regulating these so called "plant-pesticides:

> The substances that are produced in plants to protect them against pests and disease are considered to be pesticides under FIFRA . . . regardless of whether the pesticidal capabilities evolved in the plants or were introduced by traditional breeding or through the techniques of modern biotechnology. These substances, along with the genetic material necessary to produce them, are designated as "plant-pesticides" by the Agency. . . . Because of the unique characteristics of plant-pesticides, EPA recognizes that the existing [FIFRA] regulations may not always be appropriate for these products. The characteristics of plant-pesticides, such as both their production and use in plants; their biological properties; and their potential ability to spread and increase in quantity in the environment distinguishes them from traditional, chemical pesticides. The Agency therefore intends to apply the existing regulations to plant-pesticides in a manner that addresses the unique issues associated with the plants.[19]

EPA has been reviewing and registering plant pesticides since issuance of the 1994 proposed rules by applying its existing regulations for traditional chemical pesticides to govern plant-pesticides. Since 1995, EPA has registered 11 plant-pesticides. After much study and focus upon those products that posed the greatest risks to human health and the environment, EPA finally adopted rules in July, 2001 that clarified and formalized EPA's policies for regulating plant-pesticides.

B. Current FIFRA Regulation of Plant-Pesticides (40 C.F.R. Part 174).

The 2001 rules continue EPA's policy of exempting from FIFRA regulation plants that act as biological control agents due to EPA's belief that the USDA already adequately regulates such plants. Biotechnology-derived materials that enable a plant produce its own pesticide to protect itself from insects, fungi, and disease called "plant incorporated protectants", however, are subject to FIFRA and FFDCA regulation unless otherwise exempted. The 2001 rules replace the term "plant-pesticides" with "plant-incorporated protectants" or PIPs. A "plant-incorporated protectant" is defined as "a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for production of such a pesticidal substance. It also includes any inert ingredient contained in the plant, or produce thereof."[20]

Unless a PIP falls under a legal exemption, however, EPA must register it and set a food tolerance for residues of the PIP (or determine on a case-by-case basis to exempt it from the food tolerance requirement before it can be marketed). Most components of PIPs derived from genetic engineering will be subject to FIFRA and FFDCA requirements.[21] Thus, EPA will subject PIPs derived

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[19] 59 Federal Register 60,519-60,520 (November 24, 1994).

[20] *Id*. Examples of "produce thereof' include, but are limited to, agricultural produce, grains, and lumber. 40 C.F.R. § 152.3. "Genetic material necessary for the production" means both "genetic material that incodes a substance or leads to the production of a substance and regulatory regions. It does not include noncoding, nonexpressed nucleotide sequences." 40 C.F.R. § 152.3.

[21] EPA describes "genetic engineering" of PIPs as the creation of PIPs "through a process that utilizes several different modern scientific techniques to introduce a specific pesticide producing gene into a plant's DNA genetic

from genetic engineering to the more rigorous FIFRA registration process designed to ensure that such PIPs meet federal safety standards.

Certain types of PIPs are partially exempt from FIFRA regulation as a pesticide. PIPs that are derived through conventional breeding[22] from sexually compatible plants are also generally exempt from FIFRA regulation provided they meet the following two criteria:

> (i) the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance is from a plant that is sexually compatible with the recipient plant; and
>
> (ii) the genetic material has never been derived from a source that is not sexually compatible with the recipient plant.

In addition, the 2001 regulations establish an exemption from the FFDCA Section 408 requirement for both (i) residues of the pesticidal substance portion of PIPs derived through conventional breeding from plants sexually compatible with the recipient plant, and (ii) residues of any inert ingredient introduced through conventional breeding from plants sexually compatible with the recipient plant.[23] EPA also added a tolerance exemption for residues of nucleic acids that are part of the PIP.

The 2001 regulations also list the inert ingredients[24] that are exempt from FIFRA and FFDCA requirements. An inert ingredient, and residues of the inert ingredient, are exempt provided the following three conditions are met:

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material." For example, the pesticidal protein Bt can be introduced and incorporated into a plant's DNA. The plant then will produce the pesticidal protein as it would one of its own components. *Id*.

[22] EPA describes "conventional breeding" as "a method in which genes for pesticidal traits are introduced into a plant through natural methods" such as cross-pollination, bridging crosses between plants, wide crosses, and vegetative reproduction. For a [PIP], one would breed a plant that produces a pesticide with a sexually compatible plant that does not possess this property but possesses other properties of interest to the breeder, *e.g*., sweeter fruit. Then, out of the offspring, the breeder would choose the offspring plant that produces the pesticide, and therefore expresses the desired pesticidal trait, as well as producing sweeter fruit." Conventional breeding "does not include use of any of the following technologies: Recombinant DNA; other techniques wherein the genetic material is extracted from an organism and introduced into the genome of the recipient plant through, for example, micro-injection, macro-injection, micro-encapsulation; or cell fusion." *Id*.; 40 C.F.R. § 174.3.

[23] For PIPs, the recipient plant is "the living plant that receives the genetic material necessary to produce the pesticidal substance and in which the PIP is intended to be produced and used. 66 Federal Register 37,830, 37,833 (July 19, 2001).

[24] 40 C.F.R. 174.3 defines the term "inert ingredient" as "any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the genetic material necessary for the production of the substance, provided the genetic material is intentionally introduced into a living plant in addition to the active ingredient."

(a) the genetic material that encodes for the inert ingredient or leads to the production of the inert ingredient is from a plant that is sexually compatible with the recipient food plant;

(b) the genetic material has never been derived from a source that is not sexually compatible with the recipient food plant; and

(c) the residues of the inert ingredient are not present in food from the plant at levels that are injurious or deleterious to human health.

In its 2001 rulemaking package, EPA also issued a supplemental notice that it intends to consider further public comment before making final determinations on certain additional exemptions.

V. NORTH CAROLINA'S REGULATION OF PESTICIDES

The North Carolina Pesticide Law of 1971 (the "North Carolina Pesticide Law") establishes programs of pesticide management and control within North Carolina. It requires the registration of pesticide products in North Carolina, the licensing and certification of commercial and private applicators and pest control consultants, the proper handling, transportation, storage and disposal of pesticides, and the licensing of dealers selling restricted use pesticides. The North Carolina Department of Agriculture, together with the North Carolina Pesticide Board ("NCPB"), administers and enforces pesticide management rules from registration through disposal. NCDENR generally takes an administrative role for those pesticides that must be managed as hazardous wastes under the RCRA program. EPA provides North Carolina with support and oversight in enforcement of pesticide regulations and programs to train and certify pesticide applicators.

North Carolina's regulations pertaining to pesticides generally follow federal laws, predominantly FIFRA. For example, the Board has incorporated by reference the federal regulations governing tolerances for pesticides in food administered by EPA and also adopted the federal standard regarding the registration of pesticides to meet special local needs. Provided a pesticide's registration status remains unchanged and its continued use in North Carolina is in the public's best interest, state registration of a pesticide automatically renews annually.

Biotechnology companies developing new pesticide products should be aware that the NCPB has the authority to designate additional restrictions upon a pesticide's sale and use above and beyond what is required by the EPA under FIFRA. Upon finding that any pesticide is hazardous or injurious to persons, animals, or the environment, the NCPB may designate additional restrictions upon a pesticide's sale and use, such as the following: prohibiting the use of the pesticide for certain purposes and at designated times, requiring that the purchaser or user certify that the pesticide will only be used as labeled and further restricted by regulation, and requiring that all restricted use pesticides be purchased, possessed, or used only under permit of the NCPB and under its supervision in certain areas, under certain conditions, or in certain quantities. Such restrictions only may be adopted through rulemaking after a public hearing.

In addition, the North Carolina Pesticide Law prohibits any person from handling, transporting, storing, or distributing a pesticide in a manner that that will endanger humans or the environment. The disposal of any pesticide or its container must not cause injury to humans, vegetation, crops, livestock or wildlife and must not pollute any water supply or waterway.

2. United States Department of Agriculture.

Overview

In the field of agriculture, biotechnology often involves various processes, including genetic engineering, that are used to create, improve, or modify plants, animals, and microorganisms. The USDA is one of the three agencies primarily responsible for regulating biotechnology in the United States, along with the EPA and the FDA. Generally speaking, the biotechnology-related products regulated by the USDA are plants, plant pests, and veterinary biologics. The USDA's role in regulating biotechnology companies is carried out by several divisions, including the Animal and Plant Health Inspection Service ("APHIS") (which, among other things, regulates the movement and testing of genetically engineered organisms); APHIS Veterinary Biologics (which inspects biologics production facilities and licenses genetically engineered products); and the Food Safety Inspection Service (which ensures the safe use of engineered livestock, poultry and related products).

From the standpoint of most biotechnology companies, the most prominent statutory scheme enforced by the USDA is the Federal Plant Pest Act. This law regulates the movement and dissemination into the environment of "plant pests" – defined as "any living stage of: Any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances, which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants."

The USDA generally regulates biotechnology products in two categories, using two separate USDA services. First, the APHIS regulates genetically engineered plants and organisms with the potential to become "plant pests" – i.e., having the potential to adversely impact other domestic plants and/or livestock. APHIS derives this authority from the Plant Protection Act (which consolidated prior USDA/APHIS authority under statutes repealed by the Plant Protection Act). APHIS is the government's lead agency regulating the safe testing, under controlled circumstances, of biotechnology-derived, new plant varieties. A company, academic or research institution, non-profit organization or public sector scientist wishing to field test or move a biotechnology-derived plant must generally obtain APHIS approval before proceeding.

Because APHIS has concluded that genetically modified plants are generally safe, the agency has simplified its procedures for movement and field testing of "regulated articles." Most such actions are now subject only to notification procedures, and no longer require an APHIS permit. Once field tests and other relevant data have shown that an article does not pose "plant pest" risks, applicants may file for a "determination of non-regulated status," which allows the article to be commercially developed without further direct supervision from APHIS. A more detailed discussion of the APHIS program follows below.

Second, USDA's Food Safety and Inspection Service ("FSIS") approves the slaughter of

research animals for food for human consumption. Developers of genetically engineered animals must submit data to FSIS proving that the livestock and poultry involved in biotechnology experiments are not adulterated and can be sold as food along with other beef and poultry products. Research food animals are regulated by FSIS under the authority of the Federal Meat Inspection Act and the Poultry Products Inspection Act.

I. APHIS "REGULATED ARTICLES"

APHIS has regulatory authority over certain plants and organisms produced using genetic engineering, referred to as "regulated articles." 7 CFR Part 340 authorizes APHIS to regulate the "introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests." To import, move interstate, or release into the environment a genetically engineered organism or product, an individual must notify/obtain a permit from APHIS if: (1) the organism has been altered or produced through genetic engineering from a donor, vector, or recipient organism that can be classified as a plant pest or whose classification is unknown, (2) the product contains such an organism as described above, or (3) any other organism or product not included in (1) or (2) altered or produced through genetic engineering which APHIS determines is a plant pest or has reason to believe is a plant pest.

The term "plant pest" is broadly defined to include "any living stage of: any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances, which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants." Activities regulated by APHIS include the importation or interstate movement of regulated articles, or "releases into the environment," broadly defined as "the use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or a fermenter or other contained structure." Essentially, all field testing qualifies as a "release into the environment," and is under the regulatory jurisdiction of APHIS. APHIS does not assert regulatory authority over pure laboratory research.[25]

Given APHIS' broad interpretation of its regulatory authority, a responsible person should consider all genetically modified plants and crops to be "regulated articles" unless APHIS has made a determination of non-regulated status. Responsible persons that wish to challenge whether an article even meets the threshold definition of "regulated article" should consult with a member of APHIS' biotechnology staff. Despite the broad scope of regulatory authority, APHIS generally views the products of biotechnology as safe, and has steadily moved to ease its more burdensome regulations.

[25] However, greenhouses must have adequate containment controls. Researchers should consult with APHIS regarding the adequacy of containment provided by their research facilities.

II. NOTIFICATION PROCEDURES

In 1993, APHIS introduced a simplified, expedited procedure for the movement and field testing of certain regulated articles. Prior to 1993, all importation, interstate movement, and field testing of regulated articles required an APHIS permit. When APHIS first allowed notification in 1993, the agency restricted the use of notification procedures to six specific crops. In 1997, APHIS expanded eligibility for the notification process to cover almost all types of crops. In 1998, 99% of all applicants used the expedited notification process. In order to be eligible for the notification process, a regulated article must meet all of the following six criteria, as listed in 7 CFR 340.3(b):

(1) The regulated article is any plant species that is not listed as a noxious weed in regulations at 7 CFR part 360 under the Plant Protection Act (7 U.S.C. 7712), and, when being considered for release into the environment, the regulated article is not considered by the Administrator to be a weed in the area of release into the environment;

(2) The introduced genetic material is "stably integrated" in the plant genome, meaning that "the cloned genetic material is contiguous with elements of the recipient genome and is replicated exclusively by mechanisms used by recipient genomic DNA";

(3) The function of the introduced genetic material is known and its expression in the regulated article does not result in plant disease;

(4) The introduced genetic material does not:

(i) Cause the production of an infectious entity, or

(ii) Encode substances that are known or likely to be toxic to nontarget organisms known or likely to feed or live on the plant species, or

(iii) Encode products intended for pharmaceutical use;

(5) To ensure the introduced genetic sequences do not pose a significant risk of the creation of any new plant virus, plant virus-derived sequences must be:

(i) Noncoding regulatory sequences of known function, or

(ii) Sense or antisense genetic constructs derived from viral genes from plant viruses that are prevalent and endemic in the area where the introduction will occur and that infect plants of the same host species, and that do not encode a functional noncapsid gene product responsible for cell-to-cell movement of the virus;

(6) The plant has not been modified to contain the following genetic material from animal or human pathogens:

(i) Any nucleic acid sequence derived from an animal or human virus, or

(ii) Coding sequences whose products are known or likely causal agents of disease in animals or humans.

Eligible regulated articles must also meet specified performance standards, to ensure that movement and field testing through notification will pose no greater risk than through permitting. The

standards are designed to ensure containment of the introduced regulatory article and to ensure that the article or its offspring will not persist in the environment (without sustained, active, human intervention). Simply put, the performance standards are meant to be the functional equivalent of permit conditions. The performance criteria, as listed in 7 CFR 340.3(c), are as follows:

(1) If the plants or plant materials are shipped, they must be shipped in such a way that the viable plant material is unlikely to be disseminated while in transit and must be maintained at the destination facility in such a way that there is no release into the environment;

(2) When the introduction is an environmental release, the regulated article must be planted in such a way that they are not inadvertently mixed with non-regulated plant materials of any species which are not part of the environmental release;

(3) The plants and plant parts must be maintained in such a way that the identity of all material is known while it is in use, and the plant parts must be contained or devitalized when no longer in use;

(4) There must be no viable vector agent associated with the regulated article;

(5) The field trial must be conducted such that:
(i) The regulated article will not persist in the environment, and
(ii) No offspring can be produced that could persist in the environment;

(6) Upon termination of the field test:
(i) No viable material shall remain which is likely to volunteer in subsequent seasons, or
(ii) Volunteers shall be managed to prevent persistence in the environment.

Regulated entities may, but are not required to, consult with APHIS regarding what practices and procedures will be sufficient to meet the agency's performance standards.

Notifications should be directed to:

Director, Plant Protection and Quarantine
Biotechnology and Scientific Services
Animal and Plant Health Inspection Service, U.S. Department of Agriculture
4700 River Road, Riverdale Maryland 20737,

and should include the following:

(1) Name, title, address, telephone number, and signature of the responsible person;

(2) Information necessary to identify the regulated article(s), including:

(i) The scientific, common, or trade names, and phenotype of the regulated article;
(ii) The designations for the genetic loci, the encoded proteins or functions, and donor

organisms for all genes from which introduced genetic material was derived, and

(iii) The method by which the recipient was transformed;

(3) The names and locations of the origination and destination facilities for movement or the field site location for the environmental release; and the size of the introduction;

(4) The date and, in the case of environmental release, the expected duration of the introduction (release); and

(5) A statement that certifies that introduction of the regulated article will be in accordance with the provisions of 7 CFR 340.3.

Notification must be submitted to APHIS at least 10 days prior to the day of introduction of a regulated article via interstate movement, or 30 days prior to an importation or an environmental release (field test). APHIS will provide copies of notifications to the appropriate state regulatory officials within 5 business days of receipt, for their discretionary review. APHIS no longer requires that state officials affirmatively respond before the notification can be acknowledged. APHIS will provide formal acknowledgement of the notification at the end of the 10 or 30-day period. For field testing of regulated articles, the notification must be renewed annually.

Responsible persons using the notification procedures should also be aware of several affirmative obligations. Field test reports must be submitted to APHIS within 6 months after the termination of the field test. Field test reports shall include the APHIS reference number, methods of observation, resulting data, and analysis regarding all deleterious effects on plants, non-target organisms, or the environment. APHIS must also be notified of any "unusual occurrence," according to the manner and timeframe set forth in 7 CFR 340.4(f)(10) (currently, notification in writing as soon as possible but not later than within 5 working days). Finally, APHIS and state regulatory officials must be afforded access to inspect facilities, field test sites, and records in order to evaluate compliance with APHIS regulations.

III. APHIS PERMITTING

Organisms that do not qualify for the simplified notification process, most notably microorganisms and pharmaceutical-producing plants, require an APHIS permit. Because most articles do indeed qualify for the simpler notification procedures, APHIS suggests that potential applicants contact a member of APHIS' biotechnology staff to confirm that a permit is actually necessary. If a permit is necessary, applicants must provide detailed information to APHIS, as specifically set forth in 7 CFR 340.4(b). The permit application must be submitted at least 120 days in advance of any proposed release into the environment, or 60 days in advance of any interstate movement or importation. A responsible person may apply for a single permit for the interstate movement of multiple regulated articles, which shall be valid for a maximum of one year (renewals are eligible for more expedited review). Any such permit must specify all regulated articles, origin and destination points, and detailed descriptions of the facilities where regulated articles will be utilized. A new permit is required for the importation of each shipment of a regulated article.

A person who is issued a permit and his/her employees or agents shall comply with the following conditions (as listed in 7 CFR 340.4(f)), and any supplemental conditions which shall be listed on the permit, as deemed by the Deputy Administrator to be necessary to prevent the dissemination and establishment of plant pests:

- The regulated article shall be maintained and disposed of (when necessary) in a manner so as to prevent the dissemination and establishment of plant pests.

- All packing material, shipping containers, and any other material accompanying the regulated article shall be treated or disposed of in such a manner so as to prevent the dissemination and establishment of plant pests.

- The regulated article shall be kept separate from other organisms, except as specifically allowed in the permit.

- The regulated article shall be maintained only in areas and premises specified in the permit.

- An inspector shall be allowed access, during regular business hours, to the place where the regulated article is located and to any records relating to the introduction of a regulated article.

- The regulated article shall, when possible, be kept identified with a label showing the name of the regulated article, and the date of importation.

- The regulated article shall be subject to the application of measures determined by the Deputy Administrator to be necessary to prevent the accidental or unauthorized release of the regulated article.

- The regulated article shall be subject to the application of remedial measures (including disposal) determined by the Deputy Administrator to be necessary to prevent spread of plant pests.

A person who has been issued a permit shall submit to APHIS a field test report within 6 months after the termination of the field test. The report must include the APHIS reference number, methods of operation, resulting data, and analysis regarding all deleterious effects on plants, non-target organisms, or the environment.

APHIS must be notified within the time periods and manner specified below, in the event of the following occurrences:

(i) Orally notified immediately upon discovery and notify in writing within 24 hours in the event of any accidental or unauthorized release of the regulated article;

(ii) In writing as soon as possible but not later than within 5 working days if the regulated article or associated host organism is found to have characteristics substantially different from

those listed in the application for a permit or suffers any unusual occurrence (excessive mortality or morbidity, or unanticipated effect on non-target organisms).

A permittee or his/her agent and any person who seeks to import a regulated article into the United States shall:

(1) Import or offer the regulated article for entry only at a port of entry which is designated by an asterisk in 7 CFR 319.37-14(b);

(2) Notify APHIS promptly upon arrival of any regulated article at a port of entry, of its arrival by such means as a manifest, customs entry document, commercial invoice, waybill, a broker's document, or a notice form provided for such a purpose; and

(3) Mark and identify the regulated article in accordance with APHIS regulations.

APHIS regulations also include a procedure to request a "courtesy permit" for the introduction/movement of genetically engineered organisms that are not subject to APHIS regulation (in order to expedite movement/introduction of items that may appear similar to regulated articles). Applicants must include a statement explaining why they believe the article does not come within the definition of "regulated article." Applications for courtesy permits should be submitted at least 60 days in advance.

Two copies of a written application for a permit to introduce a regulated article (application form should be obtained from APHIS) shall be submitted to:

Animal and Plant Health Inspection Service, Plant Pest and Quarantine
Biotechnology and Scientific Services, Biotechnology Permits
4700 River Road, Unit 147
Riverdale, Maryland 20737-1237.

IV. PETITIONS FOR DETERMINATION OF NON-REGULATED STATUS

Generally, before a genetically engineered crop can be produced on a wider scale and sold commercially, its creators must petition APHIS for a "determination of non-regulated status," which requires the submission of more information than a field test permit request or notification. APHIS must be provided scientific details about the genetics of the plant, the nature and origin of the genetic material used, information about indirect effects on other plants, field test reports, and even information unfavorable to the petition. All petitions are published in the Federal Register and the public is given time to comment. APHIS grants the petition only if it determines that the plant poses no significant risk to other plants in the environment and is as safe to use as more traditional varieties. A successful petition means that APHIS has determined that the new plant should be treated like any other plant and, therefore, may be grown, tested, or used for traditional crop breeding without any additional APHIS action. Essentially, a favorable determination permits the plant to be widely grown and commercialized.

Applicants must include a "statement of grounds," explaining the factual grounds for their

assertion that the plant[26] should not be regulated by APHIS. Test data, copies of published and unpublished studies[27] (specifically including any unfavorable information) should be included in the submission. The applicant must certify that, to its best knowledge, the petition includes all information and views on which a determination could be based, and that the petition includes known relevant data and information unfavorable to the petition. APHIS specifically lists categories/elements of required data and information in 7 CFR 340.6(c).

The key consideration in evaluating a petition for determination of non-regulated status is whether the regulated article is likely to pose a greater plant pest risk than the unmodified organism from which it was derived. A thorough discussion of known and potential differences from the unmodified organism is required. APHIS will expect to see analysis regarding, among other items, disease/pest susceptibility, weediness, interbreeding impact, and indirect effects on other agricultural products.

After the filing of a completed petition, APHIS will publish notice in the Federal Register, triggering a 60-day notice and comment period. APHIS will furnish a response to each petitioner within 180 days of a completed petition, with a notice of availability of the decision (within APHIS' files) published in the Federal Register.

As part of its review of the petition, APHIS prepares two documents: (i) an Environmental Assessment, which details the risks of ceasing regulation of the regulated article under 7 CFR Part 340, and (ii) a Determination, which addresses whether the genetically modified article poses a plant pest risk. APHIS considers a number of factors, including wildlife impacts, whether seeds are easily dispersed in the environment, and whether the seeds can survive/persist in the environment without careful, active management. A key factor in APHIS decision making is whether the genetic engineering would alter the ability of current crops to survive outside of a managed agricultural system. APHIS will also closely scrutinize nutritional equivalency, as it could potentially impact feeding wildlife.

APHIS has also established a simpler procedure for petitions covering regulated articles that are similar to an article previously granted non-regulated status by the agency (defined in APHIS regulations as an "antecedent organism"). Such a request is referred to as an "extension to determination of non-regulated status," and is effective 30 days after APHIS' preliminary decision to grant the extension is published in the Federal Register. APHIS retains the ability to revise its decision within said 30-day period.

Applicants should submit two copies of petitions to:

Administrator
c/o Plant Protection and Quarantine

[26] APHIS clarified in the preamble to its March 31, 1993 final rule that the "petition for non-regulated status" process was designed to cover only plants, not microorganisms. Microorganisms continue to be covered by a separate section of the APHIS regulations, 7 CFR 340.5 ("Petition to Amend the List of Organisms"). 58 Fed. Reg. 17044 (Mar. 31, 1993).

[27] Petitioners may wish to check with APHIS staff to determine whether reference to published materials (rather than actual copies) would be acceptable.

Biotechnology and Scientific Services, APHIS, USDA
4700 River Road, Unit 147
Riverdale, Maryland 20737.

Non-regulated status allows for commercialization of the genetically engineered product. However, APHIS retains authority to stop the sale of the product if it is later determined that the product is indeed becoming a plant pest.

V. MARKING REQUIREMENTS FOR IMPORTATION

APHIS regulations, in 7 CFR 340.7, specify certain marking requirements for the importation of regulated articles. Articles imported by mail must be addressed and mailed to APHIS at a port of entry (designated by an asterisk in 7 CFR 319.37-14(b)), accompanied by a separate sheet of paper listing the name, address and telephone number of the intended recipient. The outer container must "plainly and correctly" list the following information:

(1) General nature and quantity of the contents;

(2) Country and locality where collected, developed, manufactured, reared, cultivated, or cured;

(3) Name and address of shipper, owner, or person shipping or forwarding the regulated article; and

(4) Number of permit authorizing the importation.

Importation by method other than by mail does not require direct delivery of the regulated article to APHIS. However, in addition to the four above-referenced items, the following must also appear on the outer container:

(1) Identifying shipper's mark and number; and

(2) Name, address, and telephone number of consignee.

Regardless of the method of importation, all regulated articles imported into the United States must be accompanied by an invoice or packing list indicating the contents of the shipment.

VI. CONTAINER REQUIREMENTS

According to APHIS regulations, regulated articles "shall not be moved" unless they comply with the container requirements of 7 CFR 340.8. The requirements vary based on the type of material that is being moved. All plants or plant parts, except seeds, cells, and subcellular elements, shall be packed in a sealed plastic bag of at least 5 mil thickness, inside a sturdy, sealed, leak-proof, outer shipping container constructed of corrugated fiberboard, corrogated cardboard, wood, or other

material of equivalent strength. Seeds must be transported in a sealed plastic bag of at least 5 mil thickness, inside a sealed metal container, which shall be placed inside a second sealed metal container. Shock absorbing cushioning material shall be placed between the inner and outer metal containers. Each metal container shall be independently capable of protecting the seeds and preventing spillage or escape. Each set of metal containers shall then be enclosed in a sturdy outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength. Regulated articles which are live (non-inactivated) microorganism, or etiological agents, cells, or subcellular elements require even more specific precautionary packaging, as set forth in 7 CFR 340.8(b)(3).

Regulated entities should also note that the APHIS container requirements are potentially not exclusive. Transport of any substances considered "hazardous" must comply with Department of Transportation hazardous material (hazmat) regulations.

3. Food and Drug Administration

When a biotechnology company decides to develop or market a product that falls under the jurisdiction of Federal Food and Drug laws, the company should expect to coordinate closely with the FDA. The extent of that relationship will, of course, be determined by the product to be marketed. For instance, the marketing of a food product will require few pre-marketing interactions, if any, with the FDA, whereas the marketing of a drug or medical device will require an intimate relationship with the FDA from the very early stages of product development through post-market monitoring for adverse effects.

The extent of the FDA's overall jurisdiction is well beyond the scope of this manuscript. As such, the goal of the following summary is to provide a general outline of the relationship that a biotechnology company can expect when developing and marketing a product that falls with the jurisdiction of the FDA.

I. FDA JURISDICTION AND STATUTORY AUTHORITY

The general purpose of the FDA is to assure that food, drugs, medical devices, and cosmetics used by consumers are safe for their intended use and bear appropriate labels. In this regard, the FDA enforces a number of statutes relating to a variety of products, including the following: the FFDCA, as amended; certain sections of the Public Health Service Act pertaining to biological products; the Radiation Control for Health and Education Act; the Safe Medical Devices Act; the Mammography Quality Standards Act; the Fair Packaging and Labeling Act; the Infant Formula Act; the Nutrition Labeling and Education Act; and, the Dietary Supplement Health and Education Act.

The regulations promulgated by the FDA are codified under CFR Title 21. The general contents of each volume of these regulations are as follows:

- Parts 1 to 99. General regulations for the enforcement of the FFDCA and the Fair Packaging and Labeling Act relating to, among other things, color additives.

- Parts 100 to 169. Food standards, good manufacturing practice for foods, low-acid canned foods, acidified foods, and food labeling.

- Parts 170 to 199. Food additives.

- Parts 200 to 299. General regulations for drugs.

- Parts 300 to 499. Drugs for human use.

- Parts 500 to 599. Animal drugs, feeds, and related products.

- Parts 600 to 799. Biologics and cosmetics.

- Parts 800 to 1299. Medical devices and radiological health. Regulations under the Federal Import Milk Act, the Federal Tea Importation Act, the Federal Caustic Poison Act, and for control of communicable diseases and interstate conveyance sanitation.

- Parts 1300 through end. Drug Enforcement Administration regulations and requirements.

Analogous or overlapping food and drug laws have been enacted by individual states, including North Carolina.

II. REGULATED PRODUCTS

The FDA has jurisdiction over a wide variety of products. The permits and approvals required for products vary and will be discussed in more detail below. Regulated products include:[28]

Foods (all kinds), including:

Vitamins
Infant Formulas
Food Additives/Food Packaging
Beverages/Bottled Water
Fishery Products
Meat and Poultry
Dairy Products
Housewares that Contact Food

Electronic Products, including:

Microwave Ovens
X-Ray Equipment
Laser Product Systems
Sunlamps

Drugs for Human Use

Cosmetics

Biological Products, including:

Vaccines
Diphtheria and Tetanus Toxoids
Skin Test Substances
Whole Blood
Blood Components for Transfusion.

Medical Devices, examples include:

Thermometers

[28] Note**:** Meat and poultry are regulated by the USDA (as well as, in North Carolina, the N.C. Department of Agriculture).

Tongue Depressors
Heating Pads
Intrauterine Contraceptive Devices
Heart Pacemakers
Kidney Dialysis Machines

Animal Products, including:

Feeds
Pet Foods
Animal Drugs
Animal Medical Devices

III. PRE-MARKET APPROVAL

Depending on the product, the FDA is involved at different levels with the development of a product and the safety evaluation prior to a product entering the market. In some cases, the FDA must grant the manufacturer, distributor or importer clearance to market certain products before they can be sold in interstate commerce. For example, new human and veterinary drugs and certain medical devices must be approved for safety and effectiveness, and their labeling reviewed for accuracy and thoroughness. The pre-market requirements for foods, drugs and medical devices will be discussed in great detail below.

Given the variety of pre-market approval requirements, it is important to identify and review those specific regulations that apply at an early stage of product development. The FDA has product specialists that can provide assistance in this area.

IV. PRE-MARKET APPROVAL FOR BIOENGINEERED FOODS

While foods generally do not require pre-market approval[29], low acid canned foods (such as canned vegetables) and acidified foods (salsas, barbecue sauces, hot sauces) must be registered with the FDA and detailed information must be submitted about heat-treatments to destroy bacteria (and acidification, if necessary to prevent growth of bacterial spores) prior to marketing. Also, if a food contains an added substance, such as coloring and preservatives, the substance must meet the requirements of food additive regulations which require sufficient scientific proof of safety and utility.

The FDA also regulates foods and feed derived from new plant varieties. FDA's biotechnology policy, issued in 1992, treats substances intentionally added to food through genetic engineering as food additives if they are significantly different in structure, function, or amount than substances currently found in food. In January 2001, the FDA proposed mandatory rules that would tighten the scrutiny of bioengineered foods. Currently, manufacturers may complete voluntary consultations on bioengineered foods. The proposal would make the current practice of voluntary consultations mandatory and require

[29] The arm of the FDA that regulates food safety is the Center for Food Safety and Applied Nutrition ("CFSAN").

manufacturers to submit safety and nutritional information to FDA. The proposed rules require that manufacturers of plant-derived, bioengineered foods and animal feeds notify the FDA at least 120 days before the products are marketed. These proposed rules also deal with the labeling of bioengineered foods under certain circumstances. The comment period for these proposed rules ended in April 2001 and a final rule is pending.

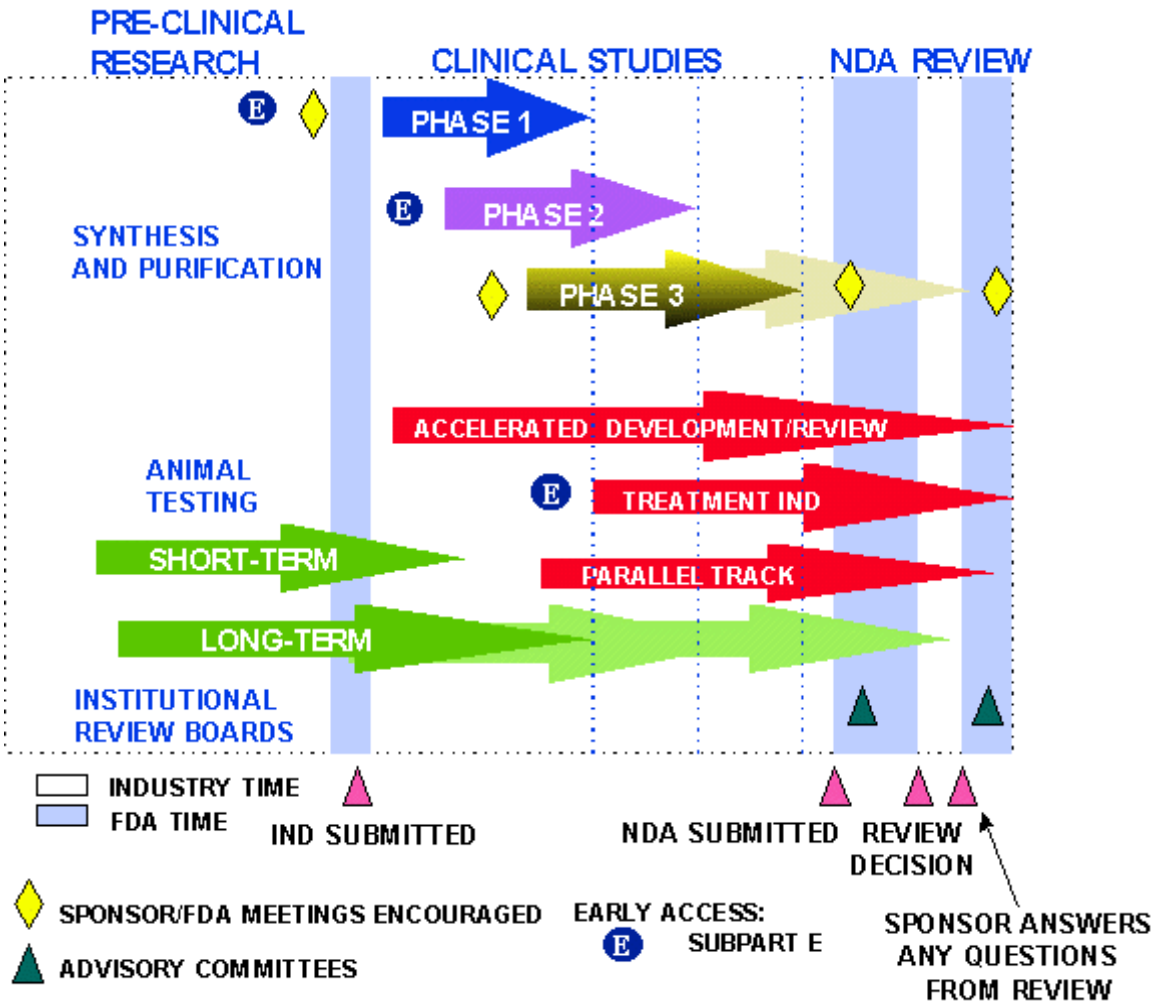
V. SAFETY EVALUATION OF DRUGS AND MEDICAL DEVICES

Because of the vital safety implications, the FDA is intimately involved with the safety evaluation of new drugs and medical devices before they are marketed. Marketing these kinds of products or conducting experimental investigations in human clinical trials requires that one or more applications be filed with the FDA at various points in the development and safety testing of the product.

A. Pre-Market Approval Requirements for Drugs[30]

The arm of the FDA that oversees drug approval is Center for Drug Evaluation and Research ("CDER"). The following diagram from the CDER's web "Handbook" provides an overview of the drug development and approval process:

[30] The approval process for Over-the-Counter drugs ("OTC") is not covered in this summary. Generally, the FDA oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks through the OTC Drug Review Program. The goal of this program is to establish OTC drug monographs for each class of products. OTC drug monographs describe acceptable ingredients, doses, formulations, and labeling for certain drugs. Products conforming to a monograph may be marketed without further FDA clearance.



1. *Investigative New Drug Application*

Before a drug manufacturer may conduct Phase I clinical trials in human subjects (see **Appendix A** for a description of each of the drug development phases), it must file an Investigative New Drug Application ("IND") with the FDA. Essentially, by filing an IND the drug manufacturer (referred to in this context as the "sponsor") is requesting an exemption from the Federal law that prohibits the interstate transport of unapproved drugs.

The main purpose of the IND is to demonstrate to the FDA that the potential new drug candidate is reasonably safe for initial use in humans and that the compound exhibits pharmacological activity that justifies commercial development. The IND application should detail the data that demonstrates that it is reasonable to proceed with certain human studies. The data provided generally includes animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information.

2. *New Drug Application*

After a sponsor has completed all research for a new drug candidate and has thereby determined that the drug is safe and commercially viable, a New Drug Application (NDA) is submitted to the FDA for final approval to market the drug.

For the FDA to approve the NDA, the evidence must indicate not only that the drug is safe, but that the drug is effective for its intended use and that the these benefits outweigh any known risks. The exact requirements for the NDA contents are a function of the nature of a specific drug. The FDA has numerous guidelines that relate to NDA content and format issues.

B. Pre-market Approval Requirements for Certain Medical Devices

The type of pre-marketing submission required for FDA approval to market a medical device is dependent on the class to which a device is assigned. The FDA has established classifications for different generic types of devices and grouped them into medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device, Class I, Class II, or Class III.

1. Pre-Market Notification

To market Class I, II and some Class III medical devices, a sponsor must submit a Pre-Market Notification, referred to as a 510(k), to the FDA at least 90 days before marketing the device unless the device is exempt from 510(k) requirements. A 510(k) is a pre-marketing submission made to the FDA to demonstrate that the device to be marketed is as safe and effective as a legally marketed device and that it is not subject to pre-market approval ("PMA") as described below. Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their claims of substantial equivalency.

2. Pre-Market Approval ("PMA")

A PMA is an application submitted to the FDA requesting approval to market a Class III medical device. Much like NDA approval discussed above, PMA approval is based on a determination by the FDA that the PMA contains sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use or uses.

While the Center for Devices and Radiological health ("CDRH") evaluates PMAs for most devices, the Center for Biologic, Evaluation, Research ("CBER") reviews submissions for medical devices associated with blood collection and processing procedures as well as those associated with cellular therapies.

VI. LABELING

One important aspect of assuring that the food and drugs used by consumers are safe involves

accurate labeling that discloses all relevant information about the product. There are very specific labeling requirements for the different types of products regulated by the FDA. For example, aside from general labeling requirements, food labels must bear certain nutritional information. Labeling requirements for a drug depend on its classification; i.e., whether it is an investigational drug, a new drug, a prescription-only drug, or an OTC drug. Drugs that are dispensed by a pharmacist are exempted from the need to use the labeling required in the manufacturer's package if the dispensed products have the pharmacist's label containing certain identifying information.

VII. OPERATIONAL STANDARDS

The practical application of FDA regulations occur by the enforcement of operational standards. There are Good Laboratory Practices ("GLP's") that apply to preclinical drug safety testing; Good Clinical Practices ("GCP's") that apply to the clinical trials in humans; and Good Manufacturing Practices ("GMP's") that apply to the manufacture of any product that falls within the jurisdiction of the FDA.

With respect to GMP's, the specific applicable standards will depend on the product that is being manufactured. Many of the operational standards are very general. This permits companies to have some level of control in deciding how best implement the processes necessary to assure the production and marketing of safe products.

A. Manufacturing (GMP's)

GMP regulations require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood control their processes in such a manner that their products are safe and uncontaminated. Noncompliance with GMP regulations can result in recalls, seizure, fines, and even incarceration.

Generally, GMP regulations cover building maintenance, record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, packaging and labeling controls, and complaint handling. Often the term "current GMP" or "cGMP" is used. This prefix is a reminder to manufacturers that they are obligated to use the most up-to-date technology in assuring adequate manufacturing controls.

B. Preclinical Research (GLP's)

GLP regulations establish standards for the conduct and reporting of nonclinical laboratory studies that will be used to support the safety evaluation of a drug candidate or medical device. The goal of GLP's is to assure the quality and integrity of safety data submitted to FDA.

The FDA relies on documented adherence to GLP requirements by nonclinical laboratories in judging the acceptability of safety data submitted in support of research and/or marketing permits. FDA has implemented a program of regular inspections and data audits to monitor laboratory compliance with the GLP requirements.

C. Clinical Research (GCP's)

GCP's are standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. Compliance with these regulations assures that the data and reported results are credible and accurate and that the rights, safety, and well-being of human clinical trial subjects are protected. The FDA has established a focal point within the agency for Good Clinical Practice issues arising in clinical trials. This unit is the Good Clinical Practice Staff in the Office of Science Coordination and Communication.

D. Documentation

Proper documentation is the key to compliance with the operational standards enforced by the FDA. The most important principles to remember with respect to documentation are:

1) If a necessary activity was not properly documented, it never occurred.

2) It is always acceptable to make necessary corrections to documentation so long as the correction is dated, initialed and does not obscure, in any way, the incorrect portion of the entry.

The FDA is very concerned with fraud when it comes to compliance with regulations. Clear and thorough documentation is the only way that the FDA can ensure that an entity is conducting its operations within proper regulatory guidelines.

E. Training of Personnel

Well-trained personnel are essential to maintaining compliance with operational standards. The FDA is always concerned with the level of training that employees have for their assigned job responsibilities. The FDA expects companies to maintain thorough and complete training records for all of their employees. Training records typically include training courses attended, including descriptions of the course topic(s) and date attended, job description for the employee, and curriculum vitae, if appropriate.

F. Contract Organizations

The reality of business today is that one entity will not necessarily conduct all phases of research, development and manufacturing for a product. Indeed, the regular use of Contract Research Organizations ("CRO") and Contract Manufacturing Organizations ("CMO") requires that companies make sure not only that their own employees are complying with FDA regulations but that any contract organization involved with a product is also in compliance. Contracts with such organizations should anticipate regulatory requirements and due diligence should put great emphasis on a candidate organization's ability to meet the requirements of all applicable regulations.

VIII. INSPECTIONS

The FDA enforces compliance with operational standards by routine and unannounced inspections of laboratories and manufacturing sites. These operational inspections are sometimes prompted by a reported problem. At the end of an investigation, the FDA investigator will issue a report of his/her findings. This report is called "Inspectional Observations" or an "FDA-483." A company must respond to any findings and take any necessary corrective actions or make changes to processes and procedures based on the FDA-483.

To help ensure that GCP standards are followed, the FDA inspects and audits the conduct and reporting of clinical trials. This program of inspections and audits, known as the Bioresearch Monitoring ("BIMO") program, covers all of the parties involved in regulated clinical trials, including clinical investigators, institutional review boards ("IRBs"), sponsors, monitors and contract research organizations. The FDA conducts more than 1000 inspections annually under this program. The FDA's clinical BIMO inspection program complements and supports the Agency's internal review of new product applications.

IX. POST-MARKET MONITORING AND RECALLS

A. Monitoring Adverse Reactions to Products

Despite the fact that thorough pre-approval testing of certain products may indicate that a product is safe, it remains difficult to predict how a product will perform after being used by a much larger population. For this reason, the FDA has extensive programs in place to monitor adverse reactions to products that fall within its jurisdiction. Reports of adverse reactions come from

consumers, health professionals, and FDA-regulated companies. An example of an FDA monitoring program is MedWatch which allows healthcare professionals and consumers to voluntarily report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.

B. Recalls

When a product is determined to be unsafe, i.e., marketed in violation of FDA requirements, it is removed from the market by recall. There are three classes of recalls:

Class I - reasonable probability that the product will cause serious adverse health consequences or death.

Class II - may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

Class III - not likely to cause adverse health consequences.

A "market withdrawal" occurs when a product has a minor violation but is otherwise not subject to FDA legal action. An example of a market withdrawal is a product that has been subjected to tampering, without evidence of manufacturing or distribution problems.

A "medical device safety alert" is issued in situations where a medical device may present an unreasonable risk of substantial harm.

X. NORTH CAROLINA FOOD, DRUG, AND COSMETIC ACT

North Carolina also has a Food, Drug, and Cosmetic Act which governs the administration of programs designed to ensure that foods, drugs, devices, and cosmetics used by consumers in North Carolina are safe, wholesome, unadulterated, properly labeled, registered, manufactured, stored, and distributed in a manner that ensures their safety and efficacy. The N.C. Food and Drug Act is administered by the N.C. Department of Agriculture. The North Carolina regulations generally adopt the federal regulations and there is significant overlap in the products and processes that are covered.

The Food Branch of the North Carolina Food and Drug Protection Division employs a program of inspection which ensures that food products are wholesome and properly labeled. This Division also monitors the quality of automotive antifreezes sold in North Carolina. The Division conducts routine unannounced inspections of food manufacturers, warehouses and distributors. Samples are routinely collected for laboratory analysis during inspections and investigations conducted when the Department receives a consumer complaint.

The Division of Federal-State Relations ("DFSR") is a division of the FDA that interacts with and serves as the focal point for cooperating state and local officials, to promote cohesive and uniform policies and activities in food and drug-related matters.

Appendix A

The Three Phases of the Drug Development Process

Phase 1

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

In Phase 1 studies, CDER can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.

Phase 2

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

In both Phase 2 and 3, CDER can impose a clinical hold if a study is unsafe (as in Phase 1), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation. *The above information is from the Center for Drug Evaluation and Research ("CDER") Handbook.*

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Smith Anderson's Biotechnology Practice

Smith Anderson regularly advises technology company clients in transactions involving life sciences. We assist our life science clients to develop, negotiate, and document a full range of transactions ranging from the earliest stages of research and development through commercialization. We also are able to assist our clients with all appropriate licensing and registration processes relevant to the technology industry. Some of the lawyers involved with our Biotechnology Practice include:

Steve Parascandola. Mr. Parascandola practices in the firm's Regulatory and Commercial Law Groups, and is the Chair of the firm's Environmental, Health & Safety Law Practice Group. His practice areas include environmental, health and safety law and litigation, life sciences and technology law, and general corporate law. Mr. Parascandola has broad experience in all aspects of environmental, health and safety law and litigation, from permitting and regulatory compliance issues to transactional and litigation matters at both the State and Federal levels. He regularly advises biotechnology and other life science clients on various aspects of TSCA, FFDCA, FIFRA, OSHA and USDA regulatory requirements. Mr. Parascandola joined Smith Anderson in 1996, after practicing for eight years with Cullen and Dykman in New York City and the North Carolina Department of Justice in Raleigh.

David Berry. Mr. Berry practices in the firm's Regulatory and Commercial Law Groups, and is a member of the firm's Environmental, Health & Safety Law Practice Group. His practice areas include environmental law and litigation, administrative and regulatory law, and life sciences and technology law. Mr. Berry has broad experience in the areas of air quality, water quality and wetlands, and OSHA issues, involving litigation and rulemaking matters as well as permitting and regulatory compliance issues at both the State and Federal levels. Mr. Berry also has significant experience in submerged lands, mining, public trust, and natural resource management issues. Mr. Berry's biotechnology law practice is focused on TSCA, FIFRA and FQPA issues. Mr. Berry joined Smith Anderson in 1998, after practicing for six years with the North Carolina Department of Justice in Raleigh

Brad Daves. Mr. Daves practices in the firm's Regulatory and Commercial Law Groups, and is a member of the firm's Environmental, Health & Safety Law Practice Group. His practice areas include environmental law and litigation, administrative and regulatory law, and life sciences and technology law. Mr. Daves has substantial experience in the areas of air quality, soil and groundwater contamination, EPCRA, renewable energy, and utility-related environmental concerns. Mr. Daves' biotechnology law practice is focused on USDA and EPCRA issues, and he received his Bachelor of Science Degree in Environmental Engineering, *magna cum laude*, from North Carolina State University. Mr. Daves joined Smith Anderson in 1999, after practicing in the Environmental Solutions Group of the McGuire Woods law firm in Washington, D.C. for approximately two years.

Candace Murphy-Farmer. Ms. Murphy-Farmer practices in the firm's Regulatory Law Group, and is a member of the firm's Environmental, Health & Safety Law and Health Law Practice Groups. Her practice areas include administrative and regulatory law and litigation, life sciences and technology law, and health law. Prior to and during law school, Ms. Murphy-Farmer worked as a research scientist in the Toxicology Division of Eli Lilly & Company, where she supervised and assisted in the design and reporting of preclinical toxicology studies to support the registration of Lilly's new drug candidates with the Food and Drug Administration. This position exposed her to a variety of regulatory issues that accompany the drug development process. Ms. Murphy-Farmer's biotechnology law practice is focused on all aspects of food and drug law, including IND/NDA, GMP, GLP, GCP and PMA matters.