EXHIBIT 8

FDA and Professional Society Materials

1. White House Office of Science and Technology Policy, Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23302 (June 26, 1986) (includes FDA Policy Statement of same date)

2. FDA, Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22984 (May 29, 1992)

3. FDA, Draft Guidance for Industry, Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering, Jan. 17, 2001 (as published on FDA.gov)

4. CQ Congressional Transcripts, House Appropriations Subcommittee Hearing, Mar. 27, 2014 (excerpt from testimony of Dr. Margaret Hamburg)

5. American Medical Association, Policy H-480.958, Bioengineered (Genetically Engineered) Crops and Foods (June 2012)

6. American Association for the Advancement of Science, Statement by the AAAS Board of Directors on Labeling of Genetically Modified Foods, Oct. 20, 2012

Coordinated Framework

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Coordinated Framework for Regulation of Biotechnology

AGENCY: Executive Office of the President, Office of Science and Technology Policy.

ACTION: Announcement of policy; notice for public comment.

SUMMARY: This Federal Register notice announces the policy of the federal agencies involved with the review of biotechnology research and products. As certain concepts are new to this policy, and will be the subject of rulemaking, the public is invited to comment on these aspects which are specifically identified herein.

DATE: Comments must be received on or before August 25, 1986.

Public Participation: The Domestic Policy Council Working Group on Biotechnology through the Office of Science and Technology Policy, is seeking advice on certain refinements published herein to the previously published proposed coordinated framework for regulation of biotechnology. These new aspects include the Biotechnology Science Coordinating Committee's (BSCC's) definitions for an "intergeneric organism (new organism)" and for "pathogen." These definitions are critical to the coordinated framework for the regulation of biotechnology because they establish the types of the organisms subject to certain kinds of review.

It is the intention of the Domestic Policy Council Working Group on Biotechnology, the Biotechnology Science Coordinating Committee (BSCC), the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA) that the policies contained herein be effective immediately. In consideration of comments, modifications, if any, may be published either in a separate notice or as part of proposed rulemaking by the involved agencies.

Information submitted to an agency that is trade secret information or confidential business information should be clearly marked so that it can be accorded the protection provided to such by each respective agency.

ADDRESS: Comments specific to the BSCC definitions or overall comments to the Coordinated Framework for the Regulation of Biotechnology statements should be addressed to: BSCC: Docket #BSCC 0001, Office of Science and Technology Policy, Executive Office of the President, NEOB-Room 5005, Washington, DC 20506.

Comments relating to the policy statements of a particular agency should be sent directly to the agency contact identified at the beginning of the respective agency policy statement.

FOR FURTHER INFORMATION CONTACT: Dr. David T. Kingsbury, Assistant Director for Biological, Behavioral, and Social Sciences, National Science Foundation, 1800 G Street, N.W., Washington, D.C. 20550, (202–357–9854).

Jerry D. Jennings,

Executive Director, Office of Science and Technology Policy

June 18, 1986

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A. Introduction

This notice describes the comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products. Specifically addressed are agency policies that formed part of the previously proposed Coordinated Framework for the Regulation of Biotechnology, published in the **Federal Register** December 31, 1984 (49 FR 50856, hereinafter "the December 84 Notice"). These agency policies build upon experience with agricultural, pharmaceutical, and other commercial products developed by traditional genetic modification techniques.

Existing statutes provide a basic network of agency jurisdiction over both research and products; this network forms the basis of this coordinated framework and helps assure reasonable safeguards for the public. This framework is expected to evolve in accord with the experiences of the industry and the agencies, and, thus, modifications may need to be made through administrative or legislative actions.

The application of traditional genetic modification techniques is relied upon broadly for enhanced characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (e.g., bacterial sewage treatment), medicine (e.g., vaccines, hormones), pesticides (e.g. *Bacillus thuringiensis*) and other uses. Federal agencies implement an array of laws which seek to ensure the safety of these products. A concise index of these U.S. laws was published in the **Federal Register** November 14, 1985 (50 FR 47174, hereinafter "the November 85 Notice"). These laws are product-specific because they regulate certain product uses, such as foods or pesticides. This approach provides the opportunity for similar products to be treated similarly by particular regulatory agencies.

Biotechnology also includes recently developed and newly emerging genetic manipulation technologies, such as recombinant DNA (rDNA), recombinant RNA (rRNA) and cell fusion, that are sometimes referred to as genetic engineering. While the recently developed methods are an extension of traditional manipulations that can produce similar or identical products, they enable more precise genetic modifications, and therefore hold the promise for exciting innovation and new areas of commercial opportunity.

Concerns were raised as to whether products resulting from the recently developed techniques would pose greater risks than those achieved through traditional manipulation techniques. For example, what might be the possible environmental consequences of the many anticipated agricultural and environmental applications that will take place outside the physical constraints of a contained facility? In particular, the environmental application of genetically engineered microorganisms may elicit concern because they are of microscopic size, and some may be able to reproduce, proliferate, and become established.

The underlying policy question was whether the regulatory framework that pertained to products developed by traditional genetic manipulation techniques was adequate for products obtained with the new techniques. A similar question arose regarding the sufficiency of the review process for research conducted for agricultural and environmental applications.

The Administration, recognizing its responsibility to confront these concerns, formed an interagency working group under the former White House Cabinet Council on Natural Resources and the Environment in the spring of 1984. The working group sought to achieve a balance between regulation

adequate to ensure health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry.

Upon examination of the existing laws available for the regulation of products developed by traditional genetic manipulation techniques, the working group concluded that, for the most part, these laws as currently implemented would address regulatory needs adequately. For certain microbial products, however, additional regulatory requirements, available under existing statutory authority, needed to be established.

The existing health and safety laws had the advantage that they could provide more immediate regulatory protection and certainty for the industry than possible with the implementation of new legislation. Moreover, there did not appear to be an alternative, unitary, statutory approach since the very broad spectrum of products obtained with genetic engineering cut across many product uses regulated by different agencies.

Because of the rapid growth in the scientific knowledge base, the working group felt strongly that the federal agencies needed to have an interagency mechanism for sharing scientific information related to biotechnology, particularly information on research and product applications submitted to the agencies.

The December 1984 Notice described the regulatory framework envisioned by the working group, and recognizing the evolutionary nature of its development, asked for comments. In summary, the Notice stated that the Food and Drug Administration (FDA) would regulate genetic engineering products no differently that those achieved through traditional techniques. The Environmental Protection Agency (EPA) described existing and proposed new policies for regulating pesticidal and nonpesticidal microorganisms. The Department of Agriculture (USDA) stated that under its different legislative authorities it could broadly regulate genetically engineered plants and animals, and plant and animal pathogens. The Notice also proposed an interagency science coordinating mechanism.

Many comments were received in response to the Notice. These contributed to the refinement of both the regulatory requirements and the interagency science coordination mechanism.

The interagency coordination mechanism, the Biotechnology Science Coordinating Committee (BSCC), discussed in more detail in section C, of this Preamble, came into being while the agencies were still in process of refining their regulatory proposals. Consequently, the BSCC was able to play a helpful role in the formulation of two basic principles: (1) Agencies should seek to adopt consistent definitions of those genetically engineered organisms subject to review to the extent permitted by their respective statutory authorities; and, (2) agencies should utilize scientific reviews of comparable rigor.

The regulatory framework anticipates that future scientific developments will lead to further refinements. Experience with earlier basic scientific research has shown that as the science progressed and became better understood by the public, regulatory regimens could be modified to reflect more complete understanding of the potential risks involved. Similar evolution is anticipated in the regulation of commercial products as scientists and regulators learn to predict more precisely particular product use that require greater or lesser controls or even exemption from any federal review.

This framework has sought to distinguish between those organisms that require a certain level of federal review and those that do not. This follows a traditional approach to regulation. Within agriculture, for example, introductions of new plants, animals and microorganisms have long occurred routinely with only some of those that are not native or are pathogenic requiring regulatory approval. It should be noted that microorganisms play many essential and varied roles in agriculture and the environment and that for decades agricultrual scientists have endeavored to exploit their advantages through routine experimentation and introduction into the environment; and as a rule these agricultural and environmental introductions have taken place without harm to the environment.

B. The Coordinated Framework for the Regulation of Biotechnology

General Comments

This notice includes separate descriptions of the regulatory policies of FDA, EPA, OSHA and USDA and the research policies of the National institutes of Health (NIH), NSF, EPA and USDA. The agencies will seek to operate their programs in an integrated and coordinated fashion and together should cover the full range of plants, animals and microorganisms derived by the new genetic engineering techniques. To the extent possible, responsibility for a product use will lie with a single agency. Where regulatory oversight or review for a particular product is to be performed by more than one agency, the policy establishes a lead agency, and consolidated or coordinated reviews. While this preamble seeks to convey an overview of the coordinated framework, it must be noted that the regulatory requirements are highly technical; reliance only on the simplified summary statements herein could be misleading and, thus, the agency policy statements must be consulted for specific details. In the event that questions arise regarding which federal agency has jurisdiction, an information contact is provided at the beginning of this notice.

While in part certain USDA and EPA requirements are new, the underlying regulatory regimens are not new. Members of the agricultural and industrial communities are familiar with the general requirements under these laws which include the Federal Plant Pest Act, The Plant Quarantine Act, the Toxic Substances Control Act (TSCA), and the Federal insecticide, Fungicide, and Rodenticide Act (FIFRA).

Because this comprehensive regulatory framework uses a mosaic of existing federal law, some of the statutory nomenclature for certain actions may seem inconsistent. Certain laws, such as USDA's Federal Plant Pest Act, require a "permit" before a microorganism pathogenic to plants may be transported or imported. Under other laws such as FIFRA, the agencies "license" or "approve" the use of particular products. TSCA requires a "premanufacturing notification (PMN)". There are also some variations among the agencies in the use of the phrase "genetic enginering." Regardless of the nomenclature, the public should be aware that the reviews conducted by each of the regulatory agencies are intended to be of comparable rigor. Agencies have agreed to have scientists from each other's staff participate in reviews. Each regulatory review will require that the safety, or safety and efficacy, of a particular agricultural or industrial product be satisfactorily demonstrated to the regulatory agency prior to commercialization.

The National Environmental Policy Act (NEPA) imposes procedural requirements on all federal agencies to prepare an analysis prior to making a decision to take any action that may significantly affect the environment. Depending on the characteristics of a proposal, an environmental assessment, or a broader environmental impact statement may need to be prepared in connection with the release of

genetically manipulated organisms. EPA's actions under most of its environmental statutes have been considered to be the functional equivalent of NEPA compliance.

For the handling of microorganisms, agencies of the Department of Health and Human Services have established recommendations for the safe use of infectious agents. The CDC/NIH publication, *Biosafety in Microbiological and Biomedical Laboratories,* describes combinations of standard and special microbiological practices, safety equipment and facilities which are recommended for working with a variety of infectious agents in research laboratories, academic and industrial. The USDA also has issued guidance on other infectious agents.

The NIH has published guidelines for the contained use of DNA organisms in the *NIH Guidelines for Research Involving Recombinant DNA Molecules,* **Federal Register,** May 7, 1986 (51 FR 16958, NIH guidelines). The guidelines recommend physical containment at specific levels for different experiments, and exempt other experiments from containment requirements. However, they recommend Biosafety Level 1, the least stringent level of physical containment, for some "exempt" experiments. For large-scale exempt experiments, the NIH guidelines recommend "Biosafety Level 1-Large-Scale" although following review by the Institutional Biosafety Committee, "some latitude" in the application of these requirements is permitted.

The appropriate large-scale containment requirements for many low risk DNA derived industrial microorganisms will be no greater than those appropriate for the unmodified parental organisms. This concept is discussed further in the Organization for Economic Cooperation and Development (OECD) document, described in the International Aspects section below.

OSHA in its **Federal Register** Notice of April 12, 1984 (50 FR 14468) stated that its authority under the Occupational Safety and Health Act of 1970 (29 U.S.C. et seq.) provides an adequate and enforceable basis for protecting the safety and health of employees in the field of biotechnology and that no additional regulation is necessary. After consideration of comments in the April 1984 notice, OSHA is publishing this policy statement in final form without change.

Product Regulation

Agencies involved with regulating agriculture, foods, medical devices, drugs, biologics and pesticides have had extensive experience with products that involve living organisms in their manufacture and/or ultimate use including releases into the environment for these purposes. By the time a genetically engineered product is ready for commercialization, it will have undergone substantial review and testing during the research phase, and thus, information regarding its safety should be available. The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens.

The regulatory scheme for products is described in Chart I *Coordinated Framework—Marketing Approval of Biotechnology Products.*

CHART I.—COORDINATED FRAMEWORK—APPROVAL OF COMMERCIAL BIOTECHNOLOGY PRODUCTS

Subject	Responsible agency(ies)
Foods/Food Additives	FDA,* FSIS.[1]
Humen Drugs, Medical Devices end Biologics	FDA.
Animal Drugs	FDA.
Animal Biologics	APHIS.
Other Contained Uses	EPA.
Plents end Animels	APHIS,* FSIS[1], FDA.[2]
Pesticide Microorgenisms Released in the Environment All.	EPA,* APHIS.[3]
Other Uses (Microorganisms):	
Intergenaric Combination	EPA,* APHIS.[3]
Intregeneric Combination:	
Pathogenic Source Organism:	
1. Agricultural Use	APHIS.
2. Non-Agricultural use	EPA,*[4] APHIS.[3]
No Pathogenic Source Organisms	EPA Report.
Nonengineered Pathogens:	
1. Agricultural Use	APHIS.
2. Non-egricultural Use	EPA,* APHIS.[3]
Nonengineered Nonpethogens	EPA Report.

*Lead agency.
[1] FSIS, Food Sefety end Inspection Service, under the Assistant Secretary of Agriculture for Marketing and Inspection Services is responsible for food use.
[2] FDA is involved when in relation to e food use.
[3] APHIS, Animal and Plent Health Inspection Service, is involved when Ina microorganism is plant pest, animal pathogen or regulated article requiring a permit.
[4] EPA requirements will only epply to environmentel releese under a "significant new use rule" that EPA intends to propose.

Jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products. The detailed description of the products and their review are found in the individual agency policy statements contained in this **Federal Register** Notice. The following is a brief summary of jurisdiction as described in Chart I.

Foods, food additives, human drugs, biologics and devices, and animal drugs are reviewed or licensed by the FDA. Food products prepared from domestic livestock and poultry are under the jurisdiction of the USDA's Food Safety Inspection Service (FSIS).

Animal biologics are reviewed by the Animal and Plant Health Inspection Service, (APHIS). APHIS also reviews plants, seeds, animal biologics, plant pests, animal pathogens and "regulated articles", i.e., certain genetically engineered organisms containing genetic material from a plant pest. An APHIS permit is required prior to the shipment (movement) or release into the environment of regulated articles, or the shipment of a plant pest or animal pathogen.

"Other contained uses" refers to the closed system uses of those microorganisms, subject the TSCA, that are intergeneric combinations, i.e., deliberately formed microorganisms which contain genetic material from dissimilar source organisms. These are subject to EPA's PMN requirement. EPA is considering promulgating a rule to exempt certain classes of microorganisms from this requirement.

Microbial pesticides will be reviewed by EPA, with APHIS involvement in cases where the pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit. (FDA may become involved in implementing pesticide tolerances for foods.)

"Other uses (microorganisms)" include uses involving release into the environment. For these, jurisdiction depends on the characteristics of the organism as well as its use. "Intergeneric combination"* microorganisms will be reported to EPA under PMN requirements, with APHIS Involvement in cases where the microorganism is also a regulated article requiring a permit.

"Intrageneric combinations" are those microorganisms formed by genetic engineering other than intergeneric combinations. For these, when there is a pathogenic [1] source organism, and the microorganism is used for agricultural purposes, APHIS has jurisdiction. If the microorganism is used for nonagricultural purposes, then EPA has jurisdiction, with APHIS involvement in cases where the microorganism is also a

[1] "Intergeneric orgeniams (new orgenisms)" end "pathogen" ere defined in section D. of the preamble.

regulated article requiring a permit. Intrageneric combinations with no pathogenic source organisms are under EPA jurisdiction although EPA will only require an informational report.

"Nonengineered pathogens" that are used for an agricultural use will fall under APHIS jurisdiction. Those that are for a nonagricultural use come under EPA jurisdiction, with APHIS involvement in cases where the microorganism is also a plant pest or animal pathogen requiring a permit. Nonengineered nonpathogenic microorganisms are under EPA jurisdiction which will require only an informational report.

Research

The coordinated framework for the regulation of biotechnology establishes requirements for the conduct of research.

Approximately ten years ago the NIH issued the NIH guidelines describing the manner in which research with organisms derived by rDNA techniques should be conducted. Since then the guidelines have been modified many times with gradual relaxation of these requirements. The guidelines prescribe the conditions under which institutions which receive NIH funds must conduct experiments. For a very small category of NIH funded experiments including environmental release, the guidelines require that the Director, NIH, approve each experiment on an individual basis. For each of these experiments, the RAC conducts a scientific review with an opportunity for public comment, and makes a recommendation to the NIH Director. As research experiments have expanded out of the biomedical area to environmental applications both agricultural and nonagricultural, other agencies have become involved, with shifting of responsibility for research approval to NSF (described in the November 85 Notice), USDA's S&E, and EPA. These other agencies' policies build, in part, on the NIH guidelines and NIH experience.

The S&E guidelines for agricultural research published separately for comment in this issue of the Federal Register have adopted the NIH guidelines with certain modifications including expansion of the scope to manipulation techniques other than rDNA; the table included with the S&E guidelines shows where particular elements of the NIH guidelines are used.

It should be noted that not all experiments involving the environmental release of genetically engineered organisms require prior federal approval. In plant applications there is a substantial body of research indicating that such experiments are of low risk. For certain categories of microorganisms modified by traditional genetic modification techniques, there is also a substantial body of research indicating low risk for environmental experiments.

Chart II—*Coordinated Fromework—Biotechnology Research Jurisdiction* shows which agency has responsibility for a particular experiment. If more than one agency has potential jurisdiction, one agency has been designated as the lead agency and it is marked with an asterisk on Chart II. The lead agency designation depends on which research agency is funding the research (e.g., NIH, S&E, or NSF) or which regulatory agency reviews specific purpose research (e.g. pesticides). In the chart and in this discussion, the authority refers to approval of the actual execution of experiments and not to their funding.

CHART II.—COORDINATED FRAMEWORK—BIOTECHNOLOGY RESEARCH JURISDICTION

Subject	Responsible agency(ies)
Contained Research, No Release in Environment:	
1. Federelly Funded	Funding agency,[1]
2. Non-Federally Funded	NIH or S&E voluntery review, APHIS.[2]
Foods/Food Additives, Human Drugs, Medical Devices, Biologics, Animel Drugs:	
1. Federally Funded	FDA*, NIH guidelines & review.
2. Non-Federally Funded	FDA*, NIH voluntery review.
Plants, Animels and Animal Biologics:	
1. Federally Funded	Funding agency,[1]* APHIS.[2]
2. Non-Federally Funded	APHIS*, S&E voluntery review.
Pesticide Microorganisms:	
Genetically Engineered:	
Intergeneric	EPA,* APHIS,[2] S&E voluntery review.
Pathogenic Intregeneric	EPA,* APHIS,[2] S&E voluntary review.
Intrageneric Nonpathogen	EPA,* S&E voluntary review.
Nonengineered:	
Nonindigenous Pathogens	EPA,* APHIS.
Indigenous Pathogens	EPA,*[3] APHIS.
Nonindigenous Nonpathogen	EPA.*
Other Uses (Microorgenisms) Released in the Environment:	
Genetically Engineered:	
Intergeneric Organisms:	
1. Federelly Funded	Funding agency,*[1] APHIS,[2] EPA.[4]
2. Commercially Funded	EPA, APHIS, S&E voluntery review.
Intrageneric Organisms:	
Pathogenic Source Organism:	
1. Federally Funded	Funding egency,*[1] APHIS,[2] EPA.[4]
2. Commercially Funding	APHIS,[2] EPA (* if non-agricul.. USE).
Intrageneric Combinetion:	
No Pathogenic Source Organisms	EPA Report.
Nonengineered	EPA Report,* APHIS.[2]

* Lead Agency.

[1] Review and approval of research protocols conducted by NIH, S&E, or NSF.

[2] APHIS issues permits for the importation and domestic shipment of certain plants and animels, plant pests and animal pathogens, and for the shipment or release in the environment of regulated articles.

[3] EPA jurisdiction for research on a plot greater than 10 acres.

[4] EPA reviews federally funded environmental research only when it is for commercial purposes.

For contained federally funded research for biomedical and agricultural purposes, research approval will be granted by the funding agency. The NIH guidelines relate primarily to biomedical experiments and only to those using rDNA techniques. Research on foods/food additives, human drugs, medical devices and biologics will continue to rely on the NIH guidelines, with NIH approval required for certain experiments such as human gene therapy, and FDA permission for clinical trials.

Fashioned after the NIH guidelines, the S&E guidelines apply to agricultural research on plants, animals, and microorganisms and provide guidance for laboratory and field testing of organisms derived using rDNA manipulation and other technologies. Adherence to the appropriate set of guidelines is required for institutions receiving financial support from NIH, S&E, or NSF. These guidelines specify what type of review procedures are required for specific categories of experiments. Some experiments require individual approval by the respective agency providing institutional support. For those experiments that require agency approval, advisory committees at NIH, S&E, and NSF, composed primarily of nongovernment scientists, may be asked to provide expert review. In addition, research on plants, animals, and animal biologics will come under APHIS permit requirements if a regulated article, plant pest, animal pathogen is involved. An APHIS permit

is required prior to the shipment (movement) or release of a regulated article, or the importation or shipment of a plant pest or regulated article used in any research experiment.

EPA has authority for all environmental research on microbial pesticides regardless of whether research is federally funded or not. EPA will regulate research under a two level review system based upon its evaluation of the potential risks posed by various types of microorganisms with lesser notification required for level I reporting and full review for level II.

For the "other uses" category from Chart II (research involving nonpesticide microorganisms released into the environment), jurisdiction for release may be under S&E, NSF, APHIS, or EPA depending primarily upon the source of the funding, but also upon the purpose of the research and the characteristics of the genetically engineered microorganism. Thus, federally funded research conducted for an agricultural use will require adherence to S&E guidelines and approval of certain experiments by S&E or NIH depending on which is the funding agency. EPA will review commercial research. APHIS's jurisdiction applies to issuing permits for regulated articles, plant pests, or animal pathogens. EPA will require an informational report for nonengineered microorganisms released into the environment, with APHIS involvement for the review of plant pests or animal pathogens.

There may be situations where one agency may choose to defer to, or ask advice from, another agency. If experiments requiring NIH, NSF or S&E review/approval are submitted for review to another agency, then NIH, NSF, or S&E may determine that such review serves the same purpose, and based upon that determination, notify the submitter that no NIH, NSF, or S&E review will take place, and the experiment may proceed upon approval from the other agency.

C. Interagency Coordination Mechanisms

The Domestic Policy Council Working Group on Biotechnology

The Domestic Policy Council Working Group on Biotechnology has been responsible for this coordinated framework for the regulation of biotechnology; it also considers policy matters related to agency jurisdiction, commercialization, and international biotechnology matters. The Working Group monitors developments in biotechnology and is ready to identify problems and make appropriate recommendations for their solution. The Domestic Policy Council Working Group on Biotechnology is a continuation of a similar group established under the former Cabinet Council on Natural Resources and the Environment.

Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there always can be potential problems and deficiencies in the regulatory apparatus in a fast moving field. The Working Group will be alert to the implications these changes will have on regulation, and in a timely fashion will make appropriate recommendations for administrative or legislative action.

The Biotechnology Science Coordinating Committee (BSCC)

The BSCC is responsible for coordination and consistency of scientific policy and scientific reviews. The BSCC, established October 31, 1985 as part of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), consists of senior policy officials of agencies involved in the oversight of biotechnology research and products. FCCSET is a statutory interagency coordinating mechanism managed by the Office of Science and Technology Policy, Executive Office of the President, with a mission to coordinate federal science activities among federal agencies. The November 85 Notice described the structure and activities of the BSCC.

One of the primary activities of the BSCC has been the development of definitions because a common scientific approach is essential to a coordinated federal regulatory framework. The underlying scientific issue, therefore, was defining those organisms subject to certain types of agency review.

The definitions are included in the following section of this preamble and have been incorporated, with modification, into the individual policy notices of the involved agencies. Explanatory material is also included in the agency policy statements. As mentioned elsewhere, the BSCC is seeking comments on these definitions.

Research to develop genetically modified organisms for environmental and agricultural applications (as for research on traditionally modified organisms) generally proceeds in a stepwise manner from highly contained facilities to progressively lesser degrees of containment as the investigator determines the safety and efficacy of experimental applications; these are conducted sequentially under controlled laboratory conditions, greenhouse testing, small field trials, and full field trials. The BSCC recognizes the need for further work to define the nature and extent of physical and biological barriers that limit or manage environmental release of modified organisms during greenhouse testing and field research.

The BSCC is authorized to hold public meetings in order to discuss public concerns about scientific and other issues. Accordingly, the BSCC will hold its first public meeting shortly after publication of this notice for discussion of the scientific aspects of this notice and the receipt of comments from the public. The public meeting will be held in July 1986. Details regarding time and location will be separately announced in the **Federal Register.**

D. BSCC Definitions

Any proposal to regulate the research and products of genetic manipulation techniques quickly confronts the issue of what organisms should be considered appropriate for certain types of review. The BSCC formulated definitions are effective immediately but are open to comment; the text following the definition of "pathogen" contains details of the request for comments.

Organisms meeting two different sets of criteria are proposed. First are organisms formed by deliberate combination of genetic material from sources in different genera. It was recognized, however, that in certain precisely constructed "intergeneric organisms" the genetic material is not considered to pose an increased risk to human health or the environment; thus, such combinations are excluded from the definition. A detailed explanation of the scientific basis for these exclusions is found in the footnote after the definition of pathogen. The BSCC specifically requests comments on whether also to consider for exclusion those organisms that exchange DNA by known physiological processes, as explained in the text immediately following the definition of "intergeneric organism (new organism)."

The second definition is "pathogen." This includes microorganisms that belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic. In certain precisely constructed modified organisms, the genetic material from a pathogenic donor is not considered to pose an increased risk to human health or the environment; and, therefore, such combinations are excluded from the definition.

The BSCC definitions of "intergeneric organism (new organism)" and

"pathogen" describe the combinations genetic material that would cause a modified organism to come under review. This does not mean to suggest that the behavior of a genetically manipulated organism exempted from these definitions is wholly predictable (since any biological organism is never 100% predictable), but that the probability of any incremental hazard compared to the unmodified organism host is low. Also, this does not mean that any product manufacture or research experiment using an organism exempted from the definition should be conducted without adherence to proper manufacturing standards or research guidelines.

Given the statutory differences in the laws that they administer, the agencies adopted the principles underlying the definitions in ways consistent with their legislation. EPA, APHIS, and S&E are using the definitions to identify levels of review for microbial products within their jurisdiction. EPA, APHIS, FDA, S&E, and NSF are using the definitions as factors to consider in the review of products or experiments.

The BSCC is attempting to define what constitutes "release into the environment." The BSCC is establishing a working group on greenhouse containment and small field trials in order to develop scientific recommendations. The concept of "containment" has traditionally been used to describe physical conditions which severely limit release (for example, a contained laboratory fermentation facility). Containment can also be "biologic" because the ability of an organism to reproduce, exchange genetic information, or become established can be effectively limited biologically. Thus, the BSCC's exploration of the conditions that constitute release into the environment will consider circumstances of both physical and biological containment for particular organisms and the circumstances of their release. While the concept of physical containment may imply the high containment conditions found in certain laboratories and greenhouses, in agricultural practice many simpler effective barriers are rountinely used; these include microplots for soil bacteria and fungi, paddocks for noninfective animals, and removing or covering the reproductive parts of plants and animals.

Release into the environment, for the time being, will have somewhat varying definitions for the regulatory and research review of the different agencies. There may be minor differences between agricultural and nonagricultural approaches and betweeen macro-and microorganisms.

Intergeneric Organism (New Organism)

Those organisms deliberately formed to contain an intergeneric combination of genetic material; excluded are organisms that have resulted from the addition of intergeneric materials that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators and ribosome binding regions.

"Well-characterized and contains only non-coding regulatory regions" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide of functional RNA molecules;

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

Pothogen

A pathogen is a virus or microorganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, microorganisms).

A microorganism (including viruses) will be subject to regulatory policies regarding pathogens if;

a. The microorganism belongs to a pathogenic species, according to sources identified by the agency, or from information known to the producer that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic according to sources identified by a federal agency, or information known to the producer and the appropriate federal agency (an example of a nonpathogenic strain of a species which contains pathogenic strains is *Escherichia cali* K–12; examples of nonpathogenic species are *Bacillus subtilis, Loctobocillus ocidohilus,* and *Soccharomyces* species); or

b. The microorganism has been derived form a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item a. above. Excepted are genetically engineered organisms developed by transferring a well-characterized, non-coding regulatory region from a pathogenic donor to a non-pathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide, or functional RNA molecules; and,

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide moldecules or act as recognition sites for the initiation of nucleic acid or protein systhesis.

This definition excludes organisms such as competitors or colonizers of the same substrates, commensal or mutualistic microorganisms, or opportunistic pathogens.

The footnote contains the scientific basis for exempting non-coding regulatory regions from the definitions of intergeneric organisms and pathogen.[2]

[2] The BSCC has based the exemption of intergeneric transfers of regulatory regions on their lack of coding capacity for the production of proteins, peptides or functional RNA molecules. It has been recommended by other members of the scientific community that there should be additional exemptions such as ribosomal proteins, ribosomal RNAs and transfer RNAs. The BSCC has chosen to examine these suggestions in more detail during the next few months. At the present the BSCC has excluded:

1. Origins of replications;
2. Ribosome binding sites;
3. Promoters;
4. Operators; and,
5. Terminators.

The basis for these exemptions is as follows. Each of these regulatory elements has no coding capacity for the production of any gene product and therefore does not promote the production of any new material. What these elements are responsible for is the initiation and modulation of nucleic acid synthesis at the specific region where they appear in the chromosome.

Bacterial genes are precisely regulated and this regulation is based on a series of regulatory elements. The principal regulatory unit is the *operon.* Operons are controlled primarily, but not exclusively, through the regulation of the rate of initiation of messenger RNA synthesis. This regulation is based on the interaction of two short nucleotide sequences in the DNA, the *promoter,* which is the site of RNA polymerase binding and the *operator,* which follows closely and acts as an off-on switch for the movement of the polymerase into the structural gene which follows. The function of the operator is to *bind* a cellular repressor protein which is synthesized in response to changing nutritional stimuli. *Terminator* regions are short nucleotide sequences which signal the termination of mRNA synthesis by the polymerase. They act as a signal for the dissociation of the polymerase from the DNA.

Replication of DNA in every biological system that has been examined is initiated at a specific site or group of sites in the chromosome. Those sites have broad specificity and a DNA molecule without the appropriate site will not be replicated. The sites which are critical to the initiation of replication are known as *origins of replication.* These regions are short nucleotide sequences which serve as initiation sites for specific enzyme action during the DNA replication process. For example, in order for mammalian DNA to replicate in bacteria, it must be associated with a bacterial origin of replication and vice versa.

Ribosome binding sites are short nucleotide segments at the beginning of messenger RNA molecules which signal the attachment of ribosomes for the initiation of protein synthesis. Functioning in this role they are not translated into the protein or peptide being processed.

The BSCC is requesting comments on these definitions during the period of sixty days following the date of this notice and specifically seeks comments addressing the following:

1. The suitability and applicability of these definitions to applications involving release into the environment, contained industrial large-scale applications, foods/food additives, drugs, medical devices, and other possible products.

2. Whether combinations of genetic material from organisms that exchange DNA by known physiological processes should be excluded from the definition of intergeneric organisms: i.e., should organisms be excluded which contain intergeneric combinations of certain specified rDNA molecules that consist entirely of DNA segments from different genera that exchange DNA by known physiological processes? As certain rDNA organisms are exempted under section III–D–4 of the NIH guidelines, the question was raised whether these organisms when used in the environment should be similarly exempted from federal product review. This exemption would not, however, exclude from review such "natural exchangers" that are also pathogens or plant pests. In the event that the exclusion of such different species that exchange DNA by known physiological processes is accepted as appropriate, a list of such species combinations that has been maintained and updated by the Office of Recombinant DNA Activities of the National Institutes of Health will be updated, in light of environmental use.

3. What are the most appropriate definitions of "release into the environment" for macro- and microorganisms.

E. International Aspects

The United States seeks to promote international scientific cooperation and understanding of scientific considerations in biotechnology on a range of technical matters. These activities add to scientific knowledge and ultimately contribute to protection of health and the environment.

The United States also seeks to reduce barriers to international trade. U.S. agencies apply the same regulation and approval procedures on domestic and foreign biotechnological products. We are seeking recognition among nations of the need to harmonize, to the maximum extent possible, national regulatory oversight activities concerning biotechnology. Barriers to trade in biotechnological products should be avoided as nations join together in working toward this mutual goal.

The U.S. agencies that have published separate policy statements as part of this notice are committed to the policy described in this section on international harmonization and have incorporated by reference the language in this International Aspects section as part of their respective agency policy statements.

Organization for Economic Cooperation and Development (OECD)

The approach of the comprehensive framework contained in this notice takes into account, *inter alia*, the broad goals described by an Ad Hoc Group of Government Experts convened by OECD in their recent report entitled, *"Recombinant DNA Safety Considerations, Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques."* The United States is pleased to have had the opportunity for its experts to work with those of other governments in the preparation of this report. The report includes the following concepts:

Summary of Major Points

Recombinant DNA techniques have opened up new and promising possibilities in a wide range of applications and can be expected to bring considerable benefits to mankind. They contribute in several ways to the improvement of human health and the extent of this contribution is expected to increase significantly in the near future.

The vast majority of industrial rDNA large-scale applications will use organisms of intrinsically low risk which warrant only minimal containment, Good Industrial Large-Scale Practice (GILSP).

When it is necessary to use rDNA organisms of higher risk, additional criteria for risk assessment can be identified and furthermore, the technology of physical containment is well known to industry and has successfully been used to contain pathogenic organisms for years. Therefore, rDNA microorganisms of higher risks can also be handled safely under appropriate physical and/or biological containment.

Assessment of potential risks of organisms for environmental or agricultural applications is less developed than the assessment of potential risks for industrial applications. However, the means for assessing rDNA organisms can be approached by analogy with the existing data base gained from the extensive use of traditionally modified organisms in agriculture and the environment generally. With step-by-step assessment during the research and development process, the potential risk to the environment of the applications of rDNA organisms should be minimized.

I. General Recommendations

1. Harmonization of approaches to rDNA technology can be facilitated by exchanging: Principles or guidelines for national regulations; developments in risk analysis; and practical experience in risk management. Therefore, information should be shared as freely as possible.

2. There is no scientific basis for specific legislation for the implementation of rDNA technology and applications. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control may be applied while avoiding any undue burdens that may hamper technological developments in this field.

3. Any approach to implementing guidelines should not impede future developments in rDNA technology. International harmonization should recognize this need.

4. To facilitate data exchange and minimize trade barriers between countries, further developments such as testing methods, equipment design, and knowledge of microbial taxonomy should be considered by both national and international levels. Due account should be taken of ongoing work on standards within international organizations such as: World Health Organization; Commission of the European Communities; International Standards Organization; Food and Agricultural Organization; and, Microbial Strains Data Network.

5. Special efforts should be made to improve public understanding of various aspects of rDNA technology.

6. For rDNA applications in industry, agriculture and the environment, it will be important for OECD Member countries to watch the development of these techniques. For certain industrial applications and for environmental and agricultural applications of rDNA organisms, some countries may wish to have a notification scheme.

7. Recognizing the need for innovation, it is important to consider appropriate means to protect intellectual property and confidentiality interests while assuring safety.

II. Recommendations Specific for Industry

1. The large-scale industrial application of rDNA technology should wherever possible utilize microorganisms that are intrinsically of low risk. Such microorganisms can be handled under conditions of Good Industrial Large-Scale Practice (GILSP).

2. If, following assessment using the criteria outlined in the document, a rDNA microorganism cannot be handled merely by GILSP, measures of containment corresponding to the risk assessment should be used in addition to GILSP.

3. Further research to improve techniques for monitoring and controlling non-intentional release of rDNA organisms should be encouraged in large-scale industrial applications requiring physical containment.

III. Recommendations Specific for Environmental and Agricultural Applications

1. Considerable data on the environmental and human health effects of living organisms

exist and should be used to guide risk assessments.

2. It is important to evaluate rDNA modified organisms for potential risk, prior to applications in agricultural and the environment. However, the development of general international guidelines governing such applications is premature at this time. An independent review of potential risks should be conducted on a case-by-case basis prior to application. Case-by-case means an individual review of a proposal against assessment criteria which are relevant to the particular proposal; this is not intended to imply that every case will require review by a national or other authority since various classes of proposals may be excluded.

3. Development of organisms for agricultural or environmental applications should be conducted in a stepwise fashion, moving, where appropriate, from the laboratory to the growth chamber and greenhouse, to limited field testing and finally, to large-scale field testing.

4. Further research to improve the prediction, evaluation, and monitoring of the outcome of applications of rDNA organisms should be encouraged.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 84N-0431]

Statement of Policy for Regulating Biotechnology Products

AGENCY: Food and Drug Administration.

ACTION: Final policy statement for regulating biotechnology products.

SUMMARY: In the Federal Register of December 31, 1984 (43 FR 50878), the Food and Drug Administration (FDA) published a policy statement for regulating biotechnology products. The policy statement was part of a larger document that included an index of U.S. laws related to biotechnology, a description of the policies of the major regulatory agencies that are involved in reviewing the products of biotechnology, a description of a proposed scientific advisory mechanism for assessment of biotechnology issues, and an explanation of how the activities of the Federal agencies involving biotechnology will be coordinated. Of the comments FDA received on the policy statement, most favored the policy statement; some requested further clarification and guidance. The current action constitutes FDA's final policy statement which has been revised in response to the comments.

ADDRESS: Written comments should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Dr. Mary Ann Danello (HF-5), Food and Drug Administration, Room 14-90, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4650.

SUPPLEMENTARY INFORMATION: FDA's policy statement of December 31, 1984 stated the FDA regulation must be based on the rational and scientific evaluation of products, and not on *a priori* assumptions about certain processes. Accordingly, FDA's administrative review of products, including those that employ specialized biotechnological techniques, is conducted in the light of the intended use of a product on a case-by-case basis. FDA believes the agency need not establish new administrative procedures to deal with generic concerns about biotechnology.

These views were supported by the majority of comments received in response to FDA's notice. Thirty-four comments were received, with 12 from manufacturers of regulated products, 16 from associations and universities, and 6 from individuals. A summary of the comments and the agency's response to them follow:

1. Many commenters urged the agency to publish additional "Points to Consider" documents to provide further guidance for biotechnology product applicants. These commenters specifically requested guidance in the area of animal drugs (especially protein drugs) and human foods and food additives.

FDA agrees that "Points to Consider" documents provide useful guidance, especially in areas involving new biotechnology, and will consider developing these documents where appropriate.

2. Related comments raised questions on FDA's general requirements for approving biotechnology products that are animal drugs, human foods, or food additives.

In response to these comments, FDA has amended the animal drug section ("General Requirements for Animal Food Additives and Drugs") to be more informative and has added a new section concerning its policies on human foods and food additives (see "General Requirements for Human Foods and Food Additives").

3. Many comments questioned the need for new or supplemental marketing applications for biotechnology products that are identical to products derived from conventional technology.

The agency has re-examined this issue and continues to believe that, as a general principle, new marketing applications will be required for most products manufactured using new biotechnology. For example, use of recombinant DNA (rDNA) technology has the potential to lead to new structural features in the product, result in product micro-heterogeneity, or introduce new contaminants (e.g., associated with new cell substrates), each of which may affect the safety, efficacy and stability of the product. Because of potential differences in the products resulting from use of recombinant DNA technology, the resulting products may be "new" products requiring separate approval under the applicable statutory provisions. However, each case will be examined separately to determine the appropriate information to be submitted. In some instances complete new applications may not be required. For example, the sponsor of a conventionally produced animal drug product who manufactures an identical or virtually identical product using biotechnology may be required to submit only a supplemental application. However, if the animal drug product manufactured using biotechnology differs significantly from the product manufactured by conventional processes, a complete original application would be required. The agency believes that each product must undergo adequate and appropriate testing and review to ensure that it is safe and effective regardless of the technology employed. Sponsors are urged to communicate with FDA to establish the scope of information required for products of biotechnology.

4. Many comments questioned the need for the proposed review mechanism by a Biotechnology Science Board (BSB). These comments stated that the additional layer of review would cause delays in the product approval process.

A notice published in the Federal Register of November 14, 1985 (50 FR 47174) discussed the establishment of the Biotechnology Science Coordinating Committee (BSCC) within the Federal Coordinating Council for Science, Engineering and Technology. That notice addressed various criticisms of the BSB. FDA believes that the new BSCC will facilitate sharing of biotechnology information among agencies and will not delay agency reviews of product applications.

In view of the foregoing, FDA's final policy statement for regulating biotechnology products reads as follows:

Introduction

A small but important and expanding fraction of the products the Food and Drug Administration (FDA) regulates represents the fruits of new technological achievements. These achievements are in areas as diverse as polymer chemistry, molecular biology, and micro-miniaturization. It is also noteworthy that technological advancement in a given area may give rise to very diverse product classes, some or all of which may be under FDA's regulatory jurisdiction. For example, new developments in recombinant DNA research can yield products as diverse as food additives, drugs, biologics, and medical devices.

Although there are no statutory provisions or regulations that address biotechnology specifically, the laws and regulations under which the agency approves products place the burden of proof of safety as well as effectiveness of products on the manufacturer. The agency possesses extensive experience with these regulatory mechanisms and applies them to the products of biotechnological processes. In this notice, FDA proposes no new procedures or requirements for regulated industry or individuals. Rather, the administrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis.

The marketing of new drugs and biologics [1] for human use, and new animal drugs, requires prior approval of an appropriate new drug application (NDA), biological product license, or new animal drug application (NADA). For new medical devices, including diagnostic devices for human use, either a premarket approval application (PMA) or reclassification petition is required. If the device is determined to be substantially equivalent to an already marketed device, a premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act) is required. For food products, section 409 of the act requires preclearance of food additives including those prepared using biotechnology. Section 706 of the act requires preclearance of color additives. The implementing regulations for food and color additive petitions and for affirming generally recognized as safe (GRAS) food substances are sufficiently comprehensive to apply to those involving new biotechnology.

Genetic manipulations of plants or animals may enter FDA's jurisdiction in other ways; for example, the introduction into a plant of a gene coding for a pesticide or growth factor may constitute adulteration of foodstuff derived from the plant, or the use of a new microorganism found in a food such as yogurt could be considered a food additive. Such situations will be evaluated case-by-case and in cooperation with the U.S. Department of Agriculture (USDA), where appropriate.

The Regulatory Process

Congress has provided FDA authority under the act and the Public Health Service (PHS) Act to regulate products regardless of how they are manufactured. Each request for product approval will be considered using the appropriate statutory and regulatory criteria. The following sections summarize general requirements for various kinds of products and address specific comments concerning particular product categories. Individual regulations should be consulted for additional details.

General Requirements for New Drugs and Biologics for Human Use

A new drug is, in general terms, a drug not generally recognized by qualified scientific experts as safe and effective for the proposed use. New drugs may not be marketed unless they have been approved as safe and effective for their intended uses. Clinical investigations on human subjects by qualified experts are a prerequisite for the determination of safety and effectiveness. Sponsors of investigations of new drugs or new uses of approved drugs file a Notice of Claimed Investigational Exemption for a New Drug (IND) to conduct clinical investigations on human subjects. The IND must contain information to demonstrate the safety of proceeding to test the drug in human subjects, including, for example, drug composition, manufacturing and controls data, results of animal testing, training and experience of investigators, and a plan for clinical investigation. In addition, assurance of informed consent and protection of the rights and safety of human subjects is required. FDA evaluates IND submissions and reviews ongoing clinical investigations. Significant changes in the conditions of the study, including changes in study design, drug manufacture or formulation, or proposals for additional studies, must be submitted to FDA as amendments to the IND.

FDA approval of an NDA or an abbreviated New Drug Application (ANDA) is required before the new drug can be marketed. The NDA must contain, among other information, the following:

- A list of components of the drug and a statement of the composition of the drug product;
- A description of the manufacturing and packaging procedures and controls for the drug product;
- A description of the nonclinical studies concerning the drug's pharmacological actions and toxicological effects;
- A description and analysis of each clinical study; and
- A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product, including commercial marketing experience.

NDA holders who intend to market an approved drug under conditions other than those approved in the NDA must submit a supplemental NDA containing clinical evidence of the drug's safety and effectiveness for the added indications. Extensive changes such as a change in formula, manufacturing process, or method of testing differing from the conditions of approval outlined in the NDA may also require additional clinical testing.

Biological products must also be approved by FDA prior to marketing, as required by section 351 of the PHS Act. A biological product is "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product * * * applicable to the prevention, treatment, or cure of diseases or injuries of man * * *." Unapproved biological products are regulated under the same regulations as new drugs during the IND phase. Prior to marketing, separate licenses are issued for the manufacturing establishment and the biological product. The manufacturing establishment and the biological product must meet standards (including any FDA standards specific for the product) designed to ensure the safety, purity, potency, and efficacy of the product. To obtain a license, the facility must also pass a prelicensing inspection. Licensed products are subject to specific requirements for lot release of FDA.

Manufacturers of new drugs and biologics must operate in conformance with current good manufacturing practice (CGMP) regulations. These

[1] FDA endorses the BSCC definitions of "intergeneric" (new) organism or "pathogen" found in the preamble, believing that they describe the microorganisms appropriate for review when environmental or agricultural applications of the microorganisms are contemplatad (and sae pp. 22–25). As discussed below in this notice, "new" drugs, biologics, medical devices, and food additives are defined in the statutes establishing FDA's jurisdiction over such products.

regulations require adequately equipped manufacturing facilities, adequately trained personnel, stringent control over the manufacturing process, and appropriate finished product examination. CGMP's are designed to protect the integrity and purity of the product.

The sponsor's process techniques are also considered in FDA's reviews and communications for the development of appropriate information on which the submission of an NDA, ANDA, or biological product license application would be based. For example, the use of recombinant DNA technology to manufacture new drugs or biological products may result in products that differ from similar products manufactured with conventional methods. Determination of the extent of testing required will depend upon the nature of the particular product. In some instances the molecular structure of the product may differ from the structure of the active molecule in nature. For example, the first human growth hormone manufactured using recombinant microorganisms has an extra amino acid, an amino-terminal methionine; hence, it is an analogue of the native hormone. Such differences could affect the drugs's activity or immunogenicity and, consequently, could affect the extent of testing required.

Another consideration in the review of new drugs or biological products producted by recombinant techniques is whether the manufacturing process includes adequate quality controls. For example, the occurrence of mutations in the coding sequence of the cloned gene during fermentation could give rise to a subpopulation of molecules with an anomalous primary structure and altered activity. This is a potential problem inherent in the production of polypeptides in any fermentation process. As with conventionally produced products, assurance of adequate processing techniques and controls is important in the manufacturing of any biotechnology-produced new drug or biological product. Review of the production of human viral vaccines routinely involves a number of considerations including the purity of the media and the serum used to grow the cell substrate, the nature of the cell substrate, and the characterization of the virus. In the case of live viral vaccine, the final product is biologically active and is intended to replicate in the recipient. Therefore, the composition, concentration, subtype, immunogenicity, reactivity, and nonpathogenicity of the vaccine preparation are all considerations in the final review, whatever the techniques employed in "engineering" the virus. However, special considerations may arise based upon the specific technology employed. For example, a hepatitis B vaccine produced in yeast (via recombinant DNA techniques) would be monitored for yeast cell contaminants, while distinctly different contaminants would be of concern in a similar vaccine produced from the plasma of infected patients.

Nucleic acids or viruses used for human gene therapy will be subject to the same requirements as other biological drugs. It is possible that scientific reviews of these products will also be performed by the National Institutes of Health.

To provide guidance to current or prospective manufacturers of drugs and biological products, the FDA has developed a series of documents describing points that manufacturers might wish to consider in the production and testing of products. The "Points to Consider" documents generated to date include several topics: interferon, monoclonal antibodies, products of recombinant DNA technology, and the use of new cell substrates. These "Points to Consider" documents are available from the agency upon request from the Office of Biological Investigational New Drugs (301–443–4864). FDA plans to develop additional "Points to Consider" in areas of scientific interest to manufacturers of new drugs and biologics.

General Requirements for Animal Food Additives and Drugs

Animal food additives and drugs are subject to similar mandatory requirements of the act as the like products for use in humans. Animal biologics, however, are licensed by the U.S. Department of Agriculture (USDA) under the authority of the Virus-Serum-Toxin Act of 1913. Questions as to whether a product is an animal biological subject to USDA licensure, or a new animal drug to be regulated by FDA are referred to a standing committee of representatives from USDA and FDA.

New animal drugs must go through the Investigational New animal Drug (INAD) and New Animal Drug Application (NADA) process, a procedure similar to that required for human drugs, as discussed earlier. However, INAD regulations do not require advance agency approval for clinical investigations for the drug, although authorization is required for use of edible products derived from food-producing animals in which the drug has been used. The data must be specific for each animal species for which the drug is intended. For NADA approval, it must be shown that the product is safe and effective when used in accordance with approved label directions. Also, it must be shown that those drugs which are intended for use in food-producing animals and used in accordance with approved label directions, do not accumulate as unsafe residues in the edible tissues of the animal at the time of slaughter. Moreover, the manufacturer must submit acceptable methods for measurement of any drug residue in edible tissues. Further, animal drugs, including premixes for use in medicated feeds and medicated feeds, must be manufactured in conformance with CGMPs. Substances that are used in animal feeds, other than drugs, and that are produced by recombinant DNA technology, are considered to be food additives and require approval of a separate food additive petition (FAP), even though a similar substance is currently approved as a food additive.

There have been questions about the requirement of an orginal application for a biotechnology product, even when the product is identical to a currently approved animal drug held by the same applicant. FDA's Center for Veterinary Medicine (CVM) has determined that, when the new substance produced by biotechnology is identical or virtually identical to an approved substance produced by conventional technology, only a supplemental application is necessary. Of course, in this instance the sponsor of the biotechnology product must also be the sponsor of the conventionally produced product. If, on the other hand, the new substance produced by biotechnology is significantly different from that produced by conventional means, an original application will be needed.

Two examples, each involving the adoption of rDNA technology as an alternative means of producing a substance that is currently the subject of an approved NADA, will illustrate. In the first example, the drug is (or appears to be) unchanged by the new production method. Under the current regulations, such a departure in manufacturing procedure requires a supplemental application which requires approval before implementation. The supplement would be a Category II supplement under CVM's supplemental policy in that it involves a revised method of synthesis or fermentation for the new drug substance. However, in accordance with the CVM's supplemental policy the underlying safety and effectiveness data

supporting the original NADA usually would not be reviewed (for compliance with contemporary standards) since there is likely no increased risk of human exposure to the drug. Data may be required to demonstrate the new animal drug product is essentially biologically equivalent to the drug product for which approval has already been granted. Approval of such a supplemental NADA is not required to be published in the **Federal Register.**

In the second example, a new method of manufacture changes the molecular structure or chemcial composition of the active ingredient. Such a change in the identity of the new animal drug normally will require an original new animal drug application and subsequent publication of a notice of approval in the **Federal Register.** Ordinarily, an original NADA requires complete safety and effectiveness studies, meeting contemporary standards. However, reference to data in another NADA sometimes suffices to support a separate NADA approval, where the existing NADA is owned by the applicant of the new NADA, or where the new applicant obtains authorization to refer to another NADA. In this case, reference might be made to data contained in the NADA supporting approval of the drug as produced by conventional means.

It may be possible to regard the new application as if it were a Category II supplement. This finding would be dependent upon data showing the new substance to be sufficiently similar to the original in terms of its pharmacology, toxicology, bioequivalence, and metabolism.

Thus, regardless of the type of application required, there is no legal requirement for the generation of new safety and effectiveness data if the applicant has access to previously submitted data, and there is no scientific need.

General Requirements for Medical Devices

Medical devices for human use are regulated by requirements of the act as amended by the Medical Device Amendments of 1976. In general, a device is a health care product that does not achieve any of its principal intended purposes by chemical action in or on the body or by being metabolized. Devices include diagnostic aids such as reagents, antibiotic sensitivity discs, and test kits for *in vitro* diagnosis of disease.

The act establishes three classes of devices: Class I (general controls), class II (performance standards), and class III (premarket approval). Classification of a device is determined by the level of regulatory control needed to provide reasonable assurance of the safety and effectiveness of the device. A class I device is a device for which the "general controls" authorized by or under various sections of the act are sufficient to provide reasonable assurance of the safety and effectiveness of a device. A class II device is a device for which general controls by themselves are insufficient to provide reasonable assurance of the Safety and effectiveness of the device, for which there is sufficient information to establish a performance standard to provide such assurance, and for which it is therefore necessary to establish a performance standard to provide reasonable assurance of its safety and effectiveness. A class III device is a device that cannot be classified into class I or class II and that is purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human, health, or that presents a potential unreasonable risk of illness or injury. Premarket approval obtained in accordance with section 515 of the act is required to provide reasonable assurance of the safety and effectiveness of a class III device.

Before a manufacturer may introduce into commerce any medical device it has not previously marketed, the manufacturer must submit to FDA a premarket notification. This notification requirement is designed to assure that manufacturers do not intentionally or unintentionally circumvent the automatic classification into class III of devices not on the market prior to enactment of the Medical Device Amendments and not substantially equivalent to pre-amendment devices.

A new device, that, is one not substantially equivalent to a pre-amendments device, remains a class III device requiring FDA approval of a premarket approval application (PMA) unless FDA reclassifies it into class I or class II, usually in response to a manufacturer's petition. In the premarket approval process the manufacturer must establish by valid scientific evidence that the device is safe and effective for its intended use. This evidence usually is data from clinical investigations.

For a significant risk device, as defined in FDA's regulations, the sponsor must submit an application to FDA for approval to conduct a clinical investigation. This application seeks an Investigational Device Exemption. When the manufacturer believes that there are sufficient data to establish the safety and effectiveness of its device, the manufacuter files a PMA.

General Requirements for Foods

Several sections of the Food, Drug and Cosmetic Act apply to the Agency's regulation of food. No particular statutory provision or regulation deals expressly with food produced by new biotechnology. Accordingly, when confronted by an issue concerning the regulation of food produced by new biotechnology, the Agency will apply the relevant statutory or regulatory provisions. Most issues concerning the safety of a food will involve the application of either section 402(a)(1) or section 409 of the Act.

Section 402(a)(1) of the Act provides, in part, that a food is adulterated if it bears or contains any poisonous or deleterious "added substance" which may render it injurious to health." Courts have agreed with the agency's interpretation of this section that any substance that is not an inherent constituent of food may be regulated as an "added substance." *See,* for example, *United States* v. *Cartons of Swordfish,* 395 F. Supp. 1194 (S.D.N.Y. 1975). Furthermore, if the quantity of the constituent exceeds the amount that would normally be present because of some technological adjustment to the product, that excess quantity may also be viewed as "added substance" within the meaning of the section. *See United States* v. *Anderson Sea Foods, Inc.,* 622 F.2d 157 (5th cir. 1980). Thus, section 401(a)(1) applies to most of the harmful substances that may occur in human food. For example, is a food produced by new biotechnology contains a higher level of a substance than it might ordinarily have, then that level "may be injurious to health" and the agency could regulate the product under section 402(a)(1). Similarly, if a food produced by new biotechnology contains, as a result of the production process, a harmful or deleterious substances not contained ordinarily in the food, the food could be in violation of the section.

The other primary statutory provisoins that FDA relies upon in determining the safety of food and food constituents are sections 201(s) and 409, the food additive provisions of the Act. The definition of food additive appears in section 201(s) of the Act and includes both artificial and natural substances. The definition provides that:

> the term food additive means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including

any source of radiation intended for any such use), if such substance is not generally recognized as safe by qualified experts.

If the substance is generally recognized as safe (GRAS) for a given food use, the product is not a food additive.

Comments questioned whether a substance (including microbes) that is GRAS could lose its GRAS status solely because it was produced or modified by new biotechnology. The answer is yes, if the substance (and its contaminants) has been altered in such a way that it can no longer be generally recognized by qualifed experts to be safe. In this instance, the substance would be a food additive and the provisions of section 409 would apply. Section 409 provides that in order to be lawfully used in food, a food additive must be the subject of an approved food additive regulation, published upon approval of a food additive petition. The FDA may not approve a food additive regulation until certain basic evidentiary criteria are met. Most important of these is that the additive must be shown to be safe under the conditions that it will be used. This requires a demonstration to a reasonable certainty that the additive will not adversely affect the health of consumers.

FDA anticipates that the techniques of new biotechnology used in producing food will, for the most part, involve rDNA and microbial isolation. The agency applies certain general principles that it will follow in determining the safety of foods produced by such techniques.

When determining the safety of food produced by rDNA techniques, the agency takes into consideration, but is not restricted to, whether:

1. The cloned DNA as well as the vector used are properly identified;
2. The details of the construction of the production organism are available;
3. There is information documenting that the inserted DNA is well-characterized [2] and free from sequences that code for harmful products, and
4. The food produced is purified, characterized, and standardized.

When determining the safety of food produced by microbial isolation, the agency will take into consideration, but is not restricted to, whether:

1. The microbial isolate used for production is identified taxonomically, and if the strain of the isolate has been genetically manipulated, whether each strain contributing genetic information to the production strain is identified;
2. The cultural purity and genetic stability of isolate has been maintained;
3. Fermentation has been performed with a pure culture and monitored for purity;
4. The microbial isolate used for production also produces antibiotics or toxins;
5. The isolates are pathogenic;[3] and
6. Viable cells of the production strain are present in the final product.

As a general rule, the extent of testing required on a food product produced by biotechnology will depend upon many factors, including the novelty of the substances used to produce the food (e.g., whether a substance is an "intergeneric" organism, as defined by the BSCC definitions in the preamble), the purity of the resulting product, and the estimated consumption of the product.

The agency will require that the final product intended for commercialization be the article tested. A complete discussion of FDA's toxicology requirements is found in the FDA publication, "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food." This publication is available through the National Technical Information Service (publication # PB 83-170696) 5285 Port Royal Road, Springfield, VA 22161. Questions concerning the publication can be directed to Dr. Alan M. Rulis in the Center for Food Safety and Applied Nutrition (CFSAN) at (301) 472-5676.

Obligations Under the National Environmental Policy Act

All premarketing approvals of FDA-regulated products are subject to the requirements of the National Environmental Policy Act (NEPA) as defined by the Council on Environmental Quality's regulations (40 CFR Parts 1500-1508) and as further described by FDA's NEPA-implementing procedures (21 CFR Part 25, final rule published April 26, 1985; 50 FR 16636). For new products or major new uses for existing products, these procedures ordinarily require the preparation of an environmental assessment. An environmental impact statement is required if the manufacture, use, or disposal of the product is anticipated to cause significant environmental impacts.

International Aspects

FDA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy General Preamble, published in today's **Federal Register.**

ENVIRONMENTAL PROTECTION AGENCY

[OPTS-00049A]

Statement of Policy; Microbial Products Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice describes how EPA is addressing certain microbial products of biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). The notice outlines EPA's plan for review of microbial pesticides under FIFRA with particular emphasis on small-scale field testing of genetically engineered, nonindigenous, and pathogenic microbial pesticides. It also announces EPA's policy for addressing new microbial products that fall under TSCA authority. This includes EPA's interpretation of the new chemical premanufacture notification (PMN)

[2] As defined by the BSCC definitions in the preamble, "well-characterized" means that the producer can document the exact nucleotide sequence of the insert and any flanking nucleotides.

[3] A pathogen is a virus or microoganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, microorganisms).

A microorganism will be included within this definition if:

a. The microorganism belongs to a pathogenic species, according to sources identified by the agency, or from information known to the producer that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as nonpathogenic according to sources identified by a federal agency, or information known to the producer and the appropriate federal agency; an example of a nonpathogenic strain of species which contains a pathogenic strain is Escherichia coli K-12; examples of nonpathogenic species are Bacillus subtilis, Lactobacillus acidophilus, and Saccharomyces species; or

b. The microorganism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item a. above. Excepted are genetically engineered organisms developed by transferring a well-characterized, non-coding regulatory region from a pathogenic donor to a non-pathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for protein, peptide, or functional RNA molecules; and,

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

This definition excludes organisms such as competitors or colonizers of the same substrates, commensal or mutualistic microorganisms, or opportunistic pathogens.

provisions of TSCA section 5 for new genetically engineered microorganisms used for commercial purposes, and the Agency's intentions to develop, under TSCA, a significant new use rule for pathogenic microorganisms; a rule modifying the PMN research and development exemption so that small scale field testing of microorganisms for TSCA purposes is subject to PMN; a section 8(a) reporting rule for other microorganisms prior to their release in the environment; and section 5(h)(4) exemptions as appropriate.

DATES: The following policies and requirements announced in this notice are effective June 26, 1986: (1) The notification and reporting requirements for small-scale field tests and the experimental use permit and registration requirements for microbial pesticides under FIFRA, described in Unit II.D of this notice; (2) premanufacture notice requirements under TSCA for "new" microorganisms, as defined in Unit III.C.1 and Unit IV of this notice, except those produced only in small quantities solely for research and development; (3) TSCA section 8(e) reporting requirements for information on substantial risks posed by microorganisms subject to TSCA, as described in Unit III.C.5 of this notice; and (4) FIFRA section 6(a)(2) reporting requirements for information on unreasonable adverse effects posed by microbial pesticides. EPA requests that persons voluntarily comply with other policies announced in this notice, as summarized in Unit I.C, until rules implementing them are promulgated.

ADDRESS: Comments on this EPA notice should be identified by Docket Number OPTS-00049A and addressed to: Document Control Officer (TS-790), Office of Toxic Substances, Environmental Protection Agency, Rm. E-201, 401 M, St. SW., Washington, DC 20460.

Information submitted as comments on this EPA notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information." Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A sanitized copy of any material containing Confidential Business Information must be provided by the submitter for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

Comments received on this notice, except those containing Confidential Business Information, will be available for review and copying from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in the TSCA Public Information Office, Rm. E-107 at the address given above.

FOR FURTHER INFORMATION CONTACT:

For general information including copies of this EPA notice and related materials: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-543, 401 M St., SW., Washington, DC 20460,Toll-free: (800-424-9065), in Washington, DC: (202-554-1404), outside the USA: (Operator 202-554-1404).

For technical information regarding the FIFRA section of the EPA policy:

By mail: Frederick S. Betz, Hazard Evaluation Division (TS-769C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

Office location and telephone number: Rm. 1128, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA (703-557-9307).

For technical information regarding the TSCA sections of the EPA policy: Anne K. Hollander, Office of Toxic Substances (TS-794), Environmental Protection Agency, Rm. E-511, 401 M St., SW., Washington, DC 20460 (202-382-3852).

SUPPLEMENTARY INFORMATION:

Table of Contents

Following is a table of contents for the EPA portion of this notice:

I. Overview

A. Purpose

For centuries, humans have used organisms to generate commercial products or to perform useful functions. During the last decade, advances in the biological sciences have increased the ability of humans to change or combine the inherited characteristics of microorganisms, plants, and animals. These advances, along with more traditional genetic engineering and biological techniques, are expected to lead to a wide variety of useful products. Among these are microorganisms that will be used to degrade toxic pollutants, leach minerals, enhance oil recovery, produce industrial chemicals, and act as pesticides. As with chemicals used for the same types of purposes, many of these microorganisms will be reviewed by EPA for potential health and environmental risks.

Specifically, EPA reviews and may register pesticide products under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and reviews chemical substances (except those used as pesticides, foods, food additives,

cosmetics, drugs, and medical devices) under the Toxic Substances Control Act (TSCA). EPA's Office of Pesticides and Toxic Substances (OPTS) is responsible for implementing both FIFRA and TSCA.

This notice describes how EPA plans to address microbial products that are subject to FIFRA and TSCA, and explains the scope of coverage and procedures for review of these products under both statutes. The following questions are addressed in this notice:

1. What microbial products are subject to review under FIFRA and how will they be reviewed? (Unit II)

2. What microbial products are subject to review under TSCA and how will they be reviewed? (Unit III)

3. What definitions will be used to identify the products that will be addressed by the appropriate statute? (Unit IV)

In reviewing products, the Agency is required under both FIFRA and TSCA to consider the potential benefits to society as well as any potential risks. EPA will take both risks and benefits into account in its regulatory decisions concerning these products, and will implement the two statutes in as consistent a fashion as possible within statutory constraints.

B. Background

1. *December 1984 proposol.* EPA issued for comment a "Proposed Policy Regarding Certain Microbial Products" as part of the Office of Science and Technology Policy's "Proposal for a Coordinated Framework for Regulation of Biotechnology." This proposal was published in the **Federal Register** of December 31, 1984 (49 FR 50880) and is hereafter referred to as the "December 84 notice." Briefly, in the December 84 notice EPA proposed a mechanism for review of genetically engineered and nonindigenous microbial pesticides under FIFRA. It also described how EPA proposed to address certain genetically engineered microorganisms subject to the new chemical substance premanufacture notification (PMN) provisions of section 5 of TSCA.

2. *Comments on the December 84 notice.* EPA received comments on the December 84 notice from 68 organizations and individuals. All the comments received by EPA are available for review and copying from 8 a.m. to 5 p.m. Monday through Friday, except legal holidays, in the TSCA Public Information Office, Rm. E-107, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

The Agency has carefully evaluated these comments. Several of the proposed policies set forth in the December 84 notice have been revised or clarified in this notice in response to these comments and as a result of the regulatory experience EPA has gained over the past year.

One of the most frequent comments addressed EPA's authority under TSCA and FIFRA. The Agency has continued to evaluate the extent and limit of its statutory authority and has concluded that TSCA and FIFRA provide sufficient authority for the Agency to meet its goals and responsibilities in regulating biotechnology products. However, some new regulations will be required and others will have to be modified in order to fully implement certain aspects of EPA's policies. These regulations and modifications are discussed in Units II and III of this notice.

Numerous commenters addressed the scope of EPA's policy and raised questions about which microbial products are subject to TSCA and FIFRA. In Units II.B, and III.B, the Agency provides detailed explanations of which microorganisms are and are not subject to FIFRA and TSCA, and from among the products that are subject, which are aubject to regulatory review prior to any environmental application.

Many commenters expreased concern that the Agency was relating a microorganism's potential for risk to the process by which it was made, particularly in the definition of which microorganisms are "new" and therefore subject to PMN under TSCA. First, commenters suggested that the process by which an organism was modified was too indirect as an indicator of its newness. They pointed out that while certain processes can be used to produce new combinations of traits in microorganisms, their use does not necessarily mean that new combinations of traits have been formed. Second, the process-based approach was believed to be an insufficient indicator of risk, because genetic engineering processes do not necessarily produce organisms that present risks, nor are non-engineered organisms necessarily safe. Finally, because the process-based approach would single out certain techniques for regulation, it would result in market distortions that favored the more traditional techniques even though the newer techniques could be as safe or safer.

After reviewing the comments, the Agency considered a number of alternatives to the "process-based" approach. In choosing among these alternatives, EPA carefully considered how well the options approximated risk (there was uncertainty with all the options in this respect), whether they could be implemented and enforced through criteria that were unambiguous to all affected persons, and (in the case of organisms subject to TSCA) the TSCA mandate to review "new" substances. The alternative EPA has chosen gives particular attention, under both FIFRA and TSCA, to microorganisms that (1) are used in the environment, (2) are pathogenic or contain genetic material from pathogens, or (3) contain new combinations of traits (e.g., organisms that are genetically modified to contain genetic material from dissimilar source organisms and organisms that are nonindigenous). EPA believes these categories have sufficiently high potential for widespread exposure, adverse effects, or uncertainty concerning potential effects to deserve particular regulatory scrutiny. This approach takes a significant step towards separating products on the basis of potential risk.

The Agency also received comments on the information and data to be submitted by companies filing notifications of intent to conduct field tests with certain microbial pesticides. These requirements have been clarified and additional references have been cited in the FIFRA unit of this notice that should provide useful guidance on what information to submit. The TSCA unit contains similar guidance on the submission of information.

Finally, several commenters addressed issues pertaining to confidential business information (CBI). Some expressed concern that CBI be adequately protected from disclosure, while others stressed the need for public access to information on new biotechnology products. EPA has summarized its position with respect to CBI and public disclosure later in this overview (Unit I.G).

A background document providing more detail on the Agency's response to comments on the December 84 notice has been placed in the public record for this notice and is available in the TSCA Public Information Office (address listed in Unit VI of this notice).

C. Summary of EPA Policy

This notice focuses on oversight and review procedures for microorganisms that are subject to FIFRA or TSCA. Microorganisms intended for use as pesticides are aubject to FIFRA, and many microorganisms intended for general commercial and environmental applications (e.g., metal leaching, pollutant degradation, enhanced nitrogen fixation) are subject to TSCA. This notice addresses the rationale for various requirements and provides guidelines for compliance.

Specifically, EPA's policies that apply to microbial products subject to FIFRA or TSCA jurisdiction will include the following specific requirements:

1. Microorganisms deliberately formed to contain genetic material from dissimilar source organisms (inter-generic) will be subject to review before any environmental releases, including small-scale field testing and other environmental research and development (R&D). Under the statute, those that are subject to TSCA and used in closed systems (i.e., never intentionally released to the environment) must be reported before they are manufactured for non-R&D commercial purposes. However, EPA is considering promulgating a rule to exempt certain contained uses from this requirement.

2. Microorganisms formed by genetic engineering other than inter-generic combinations will be subject to the following provisions: (a) if any source organism is a pathogen, the resulting microbial products are subject to review under FIFRA or TSCA prior to any environmental release, except if used solely for non-pesticidal agricultural uses, in which case they are subject only to U.S. Department of Agriculture (USDA) review (see the USDA notice in this **Federal Register**) (b) if source organisms are not pathogens, the resulting microbial products are subject to abbreviated review under FIFRA (if they are pesticides) before any small-scale environmental release, or will be subject to the reporting requirements of sections 8 (a) and (e) of TSCA.

3. Nonengineered microorganisms: (a) indigenous pathogens will be reviewed under FIFRA or TSCA prior to use on greater than 10 acres of land and greater than 1 acre of water, except those that are solely for non-pesticidal agricultural purposes, which will be subject only to USDA authority; (b) nonindigenous pathogens will be reviewed under FIFRA prior to any environmental release, and under TSCA prior to release at greater than 10 acres, unless they are pathogens used solely for non-pesticidal agricutural purposes in which case they will be reviewed by USDA (see USDA notice in this **Federal Register**); (c) nonindigenous microbial pesticides that are not pathogens will be subject to abbreviated review under FIFRA before any small scale environmental release; (d) indigenous microbial pesticides that are not pathogens will be reviewed under FIFRA prior to use on greater than 10 acres.

4. All other microorganisms used or intended for use as pesticides and not covered in Unit I.C. 1 through 3, regardless of source, mode of action, or method of manufacture will be reviewed under FIFRA prior to use on greater than 10 acres unless exempted by regulation.

5. Manufacturers and importers of microorganisms under TSCA, if they are not otherwise subject to review, will be required to submit general information, before environmental release, that the Agency can use to monitor environmental uses and to determine if additional requirements are necessary in the future. EPA will gather such information by means of a TSCA section 8(a) reporting rule.

6. Manufacturers and importers of all microorganisms subject to TSCA must report any information on substantial risks under TSCA section 8(e). Registrants of microbial pesticides must report any information regarding unreasonable adverse effects of the pesticide on the environment under FIFRA section 6(a)(2).

A table at the end of Unit I summarizes the policies for prior notification and review of microorganisms applied in the environment.

This policy is immediately effective for microbial pesticides under FIFRA and for "new" microorganisms subject to premanufacture notification under TSCA. Implementing other aspects of the policy for TSCA substances, however, will require rulemaking. Until final rules are effective, EPA expects manufacturers to comply with most aspects of the policy voluntarily. The one exception is that manufacturers of microorganisms, described in Unit I.C.5, that are excluded from other TSCA notification requirements are not expected to report until a final section 8(a) rule is promulgated.

This notice also describes the types of information EPA expects to receive from persons subject to these policies to permit an evaluation of possible risks. EPA will determine specific information needs on a case-by-case basis, and will frequently use non-Agency experts with specific knowledge of the relevant microorganisms and uses to assist in reviews. In addition, EPA is establishing a biotechnology Science Advisory Committee (SAC) to provide peer review of specific cases and advice on technical issues. The SAC will be composed of non-Agency scientists and members of the lay public. More information on the SAC may be found in Unit I.F.

Although many of the policies described in this notice are immediately effective, the Agency recognizes that biotechnology is a repidly developing field and that newly available information may affect the judgments underlying these policies. Accordingly, EPA recognizes that modifications of these policies may be necessary in the future, and it is willing to make such modifications as may be appropriate. Therefore, EPA encourages all interested persons to provide comments on the policies described in this notice. Comments should be submitted to the address provided at the beginning of this EPA notice. The public will have additional opportunities for comment when the Agency proposes rules for those parts of its policy that require rulemaking procedures. Thse parts are specifically indicated in Units II and III.

D. Rationale for Approach

This unit provides a discussion of EPA's rationale for giving special focus to environmental release, pathogens, and microorganisms with new characteristics (e.g., containing genetic material from dissimilar source organisms or nonindigenous organisms).

1. Environmental releases. Physical containment can be used to mitigate undesirable or unexpected characteristics of a microorganism by providing the means to control a microorganism's growth, reproduction, and exposure to other organisms. However, microorganisms meant to be released in the environment are not subject to this control mechanism. Although many microorganisms will be biologically contained, that is, they will have existing and inherent limitations on their growth and survival, some of them may reproduce and thereby increase in number in the environment beyond the amounts originally released. Some will also have independent mobility, or may be spread beyond the area in which they are used. Thus, to ensure that environmental releases of microorganisms do not pose unreasonable adverse effects, the Agency has determined that it should review and evaluate proposals for certain environmental releases before they are allowed to proceed. The microorganisms to be subject to review before any environmental release are described in the following paragraphs, and in Units II and III of this notice.

The Agency acknowledges the difficulty of defining environmental release. For now, the Agency's approach will focus on when an organism is considered to be contained rather than when it is released. Guidance is provided in Unit IV on how to determine whether a microorganism is considered to be contained. The definition of environmental release will be refined in subsequent rulemaking activities.

2. *Pothogenic microorganisms.* Given their ability to cause disease in plants,

animals, humans, and microbes, EPA generally believes pathogenic microorganisms should be reviewed before they are released in the environment.

As used in this notice, a "pathogen" is a microorganism that has the ability to cause disease in living organisms. This includes previously documented pathogens, and microorganisms deliberately formed to contain genetic material from pathogens (e.g., through genetic engineering techniques). A complete discussion of the definition of pathogenicity is included in Unit IV, as well as guidance to aid in the determination of whether a particular microorganism falls within the scope of the EPA policies that address pathogens.

Pathogens are a clearly defined category of organisms known to cause adverse effects. In addition, because of the increased uncertainty about behavioral changes that may be associated with genetically engineered pathogens, the Agency has decided to review genetically engineered pathogens prior to any environmental release (including small-scale field testing). However, the Agency will defer review of nonengineered indigenous pathogens until they are used in larger scale applications (greater than 10 acres), because ample experience indicates that nonengineered, indigenous pathogens are sufficiently well controlled by natural mechanisms in small-scale environmental applications. Further, the Agency will not review pathogens used solely for non-pesticidal agricultural purposes (except those formed through inter-generic combinations, which are "new") because these are adequately reviewed by the USDA (see the USDA notice in this Federal Register).

The Agency's decision to focus on pathogens does not mean that EPA has concluded that nonpathogens are necessarily safe or that all pathogens present unreasonable risks. In fact, the Agency expects to identify widely varying degrees of risk among different uses of pathogens. It should be clear that other considerations besides pathogenicity will affect the evaluation of risk, e.g., functions of the recombined genes, possibilities for genetic transfer, environmental fate, and potential competition with other organisms. When other considerations indicate that it is appropriate, the Agency will consider excluding specific categories of pathogens from review, or may provide guidance that would limit the information requirements associated with its reviews of pathogens. As explained in Unit IV, the Agency has already exempted from review as pathogens organisms that incorporate only certain genetic material from pathogens.

3. *Microorganisms with new characteristics.* A third factor that makes potential adverse effects of microorganisms less predictable is the existence of new traits or characteristics. These traits may be new to the organism, or new to the environment in which the organism is released.

a. *Microorganisms having significant potential to exhibit new traits.* Modern genetic engineering techniques permit genetic material to be intentionally combined in organisms that would not normally share that genetic material. Some of these genetically engineered microorganisms may exhibit new or altered traits affecting, for example, their survivability, host range, substrate utilization, competition with other organisms, or protein or polysaccharide production. In some cases such microorganisms may be able to evade or overcome natural controls on their growth, or controls on their ability to cause adverse effects. In many other cases, their natural hardiness will be reduced.

In addition to the possibility that certain engineered organisms may exhibit new traits, if they are released they may be transported through natural dispersal mechanisms to other areas in the environment that have not previously contained organisms having these new combinations of traits.

Because of these considerations, EPA's policies will give particular regulatory attention to organisms that have a significant probability of exhibiting a new trait or combination of traits (standards for this are explained below). This approach accomplishes two important objectives. First, it identifies a group of microorganisms whose behavior in the environment poses significant uncertainty and thus warrants regulatory review. Simultaneously, it provides a way of defining "new" microorganisms that are subject to PMN requirements under TSCA (see Unit III.C.1).

EPA's policy, specifically, focuses on microorganisms that have been deliberately altered to contain genetic material from dissimilar source organisms, because such organisms are more likely to exhibit new combinations of traits and their behavior is therefore less predictable. Given this conceptual basis, the question then becomes how dissimilar two organisms must be before combinations of genetic material between them are likely to produce "new combinations of traits."

Based on the following considerations, EPA has decided that inter-generic combinations (combinations from source organisms of different genera) but not intra-generic combinations (source organisms from the same genus) are sufficiently likely to result in new combinations of traits that they should be given special attention. First, combinations of genetic material from microorganisms from different genera are more likely to result in new traits than combinations of genes from microorganisms within the same genus. Also, while genetic exchange occurs naturally and somewhat commonly among many microorganisms, it is more likely to occur in nature within a single genus than across many different genera (Refs. 2, 12, 13). Finally, genus designations provide a practical criterion for administrative and regulatory purposes.

The Agency has decided to exclude certain combinations from special consideration as inter-generic organisms. Excluded are inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. The resulting organisms do not possess new combinations of traits; rather, they exhibit quantitative changes in preexisting traits. In addition, if experience or data indicate that certain other inter-generic combinations warrant exclusion, the Agency will use the appropriate statutory or policy mechanisms under FIFRA and TSCA to waive certain requirements for reviewing them. For example, EPA is considering exempting from PMN review under TSCA those inter-generic combinations used only in physically contained systems.

Although EPA considers intra-generic combinations to be less likely to produce new combinations of traits than inter-generic combinations, the Agency realizes that science provides no absolute standard for such distinctions. Nevertheless, EPA believes the approach it has adopted is practical and facilitates the identification of those microorganisms that should be subject to special attention and also that should be considered "new" under TSCA. If experience reveals that intra-generic combinations that could cause adverse effects will be developed, the Agency will modify its policies to require review of these products.

Unit IV contains more detailed guidance for determining if a given microorganism is the result of an inter-generic combination. The determinations are based on taxonomic

designations of organisms. The Agency is aware that microbial taxonomy is a dynamic and often controversial science (Refs. 4, 18) and that new information concerning microorganisms' properties and interrelationships will alter taxonomic designations. However, the Agency believes that its procedures can be sufficiently flexible to accommodate the developments that will occur, and that there are many significant advantages to using taxonomic standards. These advantages are discussed in more detail in Unit IV.

b. *Nonindigenous microorganisms.* Another category of organisms that are likely to exhibit traits new to an environment is nonindigenous microrganisms. Application of nonindigenous microorganisms in the environment could pose a high degree of uncertainty with respect to their behavior. Experience shows that scientists cannot always accurately predict how such organisms will behave in their new environment (Ref. 15, 16). It can be difficult to predict whether a nonindigenous microorganism will be subject to the physical and biological control factors present in the environment where it is to be introduced. In a small number of cases, nonindigenous pathogens such as the chestnut blight fungus and the Dutch elm disease fungus have caused significant adverse effects. As a result, there exist today regulations that govern the intentional movement of some, but not all, nonindigenous species (e.g., the Plant Pest Act administered by USDA). EPA believes that nonindigenous microorganisms whose uses are covered by FIFRA should be subject to Agency review and evaluation before they are released in the environment, to minimize the uncertainties with respect to their behavior. However, EPA does recognize that small-scale use of certain nonindigenous microbial pesticides (i.e., pathogens) may pose greater potential risk than others, and has accordingly adopted abbreviated review procedures for small-scale use of nonpathogenic nonindigenous microbial pesticides. Unit II addresses these issues, and Unit IV provides guidance on determining whether a microorganism is nonindigenous.

E. Explanation of Jurisdiction—EPA and USDA

Both EPA and USDA seek to assure the safety of microbial products and yet minimize impediments to intellectual and economic advances in biotechnology. Because some of the statutes the agencies administer entail overlapping responsibilities, the two agencies are eliminating duplicative requirements wherever possible and coordinating their reviews.

Where allowed by statute, EPA and USDA have sought to eliminate overlapping reviews altogether. This notice reflects many instances where this has been done. Where overlaps could not be avoided, the agencies have established mechanisms for coordinating their reviews. EPA and USDA will identify principal liaisons who will have the responsibility to share information, coordinate data requests, and keep one another informed of communications with submitters. Also, the agencies will form a coordinating committee to meet periodically and work out general coordination problems that may transcend specific reviews. Finally, the National Biological Impact Assessment Program that has been established within USDA will provide a common resource of scientists available to both agencies to review procedures, protocols, and projects on an advisory basis.

Submitters are encouraged to contact either agency if they have jurisdictional questions, but general guidelines are described below.

First, inter-generic microorganisms containing genetic material from a pathogenic source organism must be reported to both agencies (definitions of "inter-generic" and "pathogen" may be found in Unit IV). In this case, statutory constraints make it necessary for both EPA and USDA to review the products because the microbes are potential "pests" subject to the Plant Pest Act, and they are "new" and therefore subject to TSCA premanufacture notification (or they are pesticides and subject to FIFRA notification). However, the agency reviews have somewhat different purposes, in that the EPA review is for a general use of an organism under TSCA or for use as a pesticide under FIFRA, while the USDA review is for a specific permit application. The agencies will coordinate these reviews as explained earlier.

Second, persons developing inter-generic organisms that contain no genetic material from a pathogen and that do not meet the USDA definition of a "plant pest" will be expected to report only to EPA; they will not report to USDA at all. EPA will inform USDA and the submitter if any data suggest that the organism has pest qualities which may require a permit from USDA. This avoids unnecessary duplication of effort and is consistent with the non-discretionary responsibility under TSCA to review new organisms and under FIFRA to review pesticides.

Third, in the case of intra-generic engineered organisms that contain genetic material from a pathogen, the use of the organism will determine which agency reviews it. When used solely for non-pesticidal agricultural purposes, such organisms must be reported only to USDA under the Plant Pest Act. When used for non-agricultural purposes, such organisms should be reported to EPA, either voluntarily under the TSCA section 5(a)(2) rule EPA will be developing or, if the organism is a pesticide, under FIFRA. In both cases, the microorganisms should also be reported to USDA as potential plant or animal pathogens. When such dual reporting is necessary, the agencies will assist the submitter by coordinating through the mechanisms described above.

In the case of intra-generic microbes containing no genetic material from pathogens and nonengineered microorganisms, EPA will gather general information under section 8(a) of TSCA and conduct abbreviated reviews under FIFRA (see Units II and III of the EPA notice). Both agencies agree that members of this category of microbes, in general, present the lowest risk and therefore do not need a high level of scrutiny before any release into the environment. However, the FIFRA abbreviated reviews and the TSCA section 8(a) reporting will ensure that both agencies are aware of environmental releases of these organisms and can take appropriate action when necessary.

F. EPA Biotechnology Science Advisory Committee

EPA is establishing a Science Advisory Committee for biotechnology. The formation of this committee is consistent with intentions stated in two **Federal Register** notices issued by the Office of Science and Technology Policy (49 FR 50904, December 31, 1984 and 50 FR 47174, November 14, 1985). The committee's primary functions will be to provide peer review of specific product submissions under TSCA, FIFRA, and other EPA statutes and scientific oversight of the Agency's biotechnology programs.

The committee will consist of independent scientists and members of the lay public. It will be of sufficient size and diversity to provide the range of expertise required to assess the scientific and technical issues pertinent to its responsibilities. The committee will be supplemented by consultants when they are needed to extend the range of expertise of the standing committee, and will be authorized to

form subcommittees or panels for any purpose consistent with its charter.

Scientific members of the committee will be selected on the basis of their professional qualifications to examine the questions of hazard, exposure, and risk to humans, other non-target organisms, and ecosystems. Some committee members will serve as liaisons (holding joint membership) with the FIFRA Scientific Advisory Panel (SAP) and with the EPA Science Advisory Board (SAB). The SAC will also include nonvoting representatives from other Federal agencies that are involved in regulating products of biotechnology.

The Agency intends for meetings of the SAC to be open to the public. Meetings may be closed by the Chairperson when necessary, such as during discussion of issues subject to statutory confidentiality requirements, but EPA will encourage open public discussion of issues to the greatest extent possible (see unit I.G).

G. Confidential Business Information

Both FIFRA and TSCA generally prohibit the Agency from releasing certain confidential business information (CBI). These prohibitions apply to information on products of biotechnology, and the Agency will meet its obligations to protect information claimed confidential by applicants and other data submitters. However, the Agency also recognizes that there is strong public interest in many aspects of biotechnology, particularly in the possibility of adverse effects resulting from the environmental release of genetically engineered organisms. Accordingly, it is the Agency's policy to carry out as much of its review as possible in the open, in order to provide an opportunity for public participation and to increase public confidence in the review process. The Agency is encouraged by the extent to which industry and other submitters have been willing to authorize the release of relevant information to date and urges future data submitters to limit confidentiality claims as much as possible in order to foster an open review process.

H. International Aspects

EPA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy Preamble, published in this Federal Register.

SUMMARY TABLE.—PRIOR NOTIFICATION AND REVIEW OF MICROORGANISMS APPLIED IN THE ENVIRONMENT

[Coverege by notification and review policy [1]]

Type of microbial product	FIFSRA		TSCA	
	< 10 acres	>10 acres	< 10 acres	> 10 acres
1. Genetically engineered microorganisms				
a. Formed by deliberate combinations of genetic material from dissimilar source organisms (inter-generic combinations).	X	X	X	X
b. Formed by genetic engineering other than inter-generic combinations				
i. pathogenic source organisms [2]	X	X	X	X
ii. nonpathogenic source organisms	O	X	O	O
2. Nonengineered microorgenisms				
a. Nonindigenous pathogens [2]	X	X	O	X
b. Nonindigenous nonpathogens	O	X	O	O
c. Indigenous pathogens [2]		X	O	X
d. Indigenous nonpathogens		X	O	O

[1] "X" designates that the microorganism will be subject to EPA review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under TSCA, submitters would only notify the Agency once (at the first appropriate time), unless during the original review EPA specifies that further reporting is required.
"O" designates that the microorganism will be subject to abbreviated review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under FIFRA, this provision is effective immediately. Under TSCA, the abbreviated notification will be implemented through rulemeking.
[2] Pathogens in this category used solely for non-pesticidal agricultural purposes will not be subject to EPA notification requirements. They will be subject only to USDA review. See Unit IV for a definition of "agricultural uses" and "pathogens."

II. Applicability of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to Microbial Products

A. Background

Biological agents, including microorganisms, may be used as pesticides, and as such they are subject to regulation under FIFRA unless specifically exempted by regulation. FIFRA establishes EPA's authority over the distribution, sale, and use of pesticide products. Before EPA can register a pesticide, it must have sufficient data to determine that the product, when used in accordance with widespread and commonly recognized practice, will not cause (or significantly increase the risk of) unreasonable adverse effects to humans or the environment. In recent years, the Agency has put in place policies, procedures, and regulations to address the human health and environmental concerns raised by the application of biological pesticides (including genetically engineered and nonindigenous microbial products) in the environment. This unit outlines EPA's regulatory mechanism for these products and updates its policy on small-scale field testing of microbial pesticides.

Regulations promulgated under FIFRA and appearing at 40 CFR 162.5(c)(4) specify that microorganisms, when used as pesticides, are regulated under FIFRA. The specific kinds of data and information that are required to support the registration of each microbial pesticide under FIFRA are detailed in 40 CFR 158.65, 158.170, and 162.163. The Agency has also published guidance for developing these data in the Pesticide Assessment Guidelines: Subdivision M—Biorational Pesticides (Ref. 20).

The Agency must conduct a complete evaluation and review of the data submitted to support any pesticide registration before determining whether the pesticide should be registered. This evaluation is conducted with respect to the general criteria set forth in 40 CFR 162.7(d) and (e) and 162.167. Prior to registration, producers may test their pesticide products under an experimental use permit (EUP), issued pursuant to section 5 of FIFRA and 40 CFR Part 172. The data and information needed to support the issuance of an EUP for microbial pesticides are specified at 40 CFR 158.170.

The regulations governing EUPs include a generally applicable presumption that EUPs will not be required for certain small-scale experimental uses of new pesticides (or new uses of previously registered pesticides). Recently, however, the Agency issued a statement of interim policy on small-scale field testing of nonindigenous and genetically altered microbial pesticides, published in the Federal Register of October 17, 1984 (49 FR 40659); see also 49 FR 50882, December 31, 1984. Briefly, the policy statement announced that the small-scale field test provision of 40 CFR 172.3 would not automatically apply to, and that the Agency should be notified before the initiation of, any field testing of genetically altered or nonindigenous microbial pesticides to determine if EUPs are required. This policy is being revised by this notice and is discussed in detail in Unit II.D.

B. Scope of FIFRA

1. *Pesticides addressed by this notice.* All pesticides whose active ingredient(s) consist of microorganism(s) (i.e., all microbial pesticides) are addressed by

this notice. Microbial pesticides may include bacteria and blue-green algae, fungi, viruses, and protozoa used as pest control agents.

2. *Pesticides not addressed by this notice.* The Agency has determined that certain nonmicrobial organisms which fall within the definition of biological control agents are already addressed by other agencies, specifically USDA and the Department of the Interior. Examples of these biological control agents are vertebrates, insect predators, nematodes, and macroscopic parasites. Therefore, pursuant to section 25(b) of FIFRA and 40 CFR 162.5(c)(4), these nonmicrobial biological control agents have been exempted from regulation under FIFRA. However, if EPA, in cooperation with other agencies, determines that certain biological control agents exempted by § 162.5(c)(4) are not being adequately regulated, these organisms will be referred to the attention of the appropriate agency or added to the exceptions in § 162.5(c)(4) by amendment. In the latter case, those organisms would no longer be considered exempt from the provisions of FIFRA.

This unit of the notice does not address any chemical pesticide product or byproduct produced by microorganisms. Such chemicals are covered under current pesticide regulations, registration procedures, data requirements, and testing guidelines (see 40 CFR Parts 158 through 180; and Subdivisions D through O of the Pesticide Assessment Guidelines).

3. *Information-gathering policy.* In order to expand its level of knowledge and expertise, monitor the industry, and determine whether its current policy needs modification, the Agency needs as complete a data base as possible. Accordingly, those developing microbial products intended for use as pesticides that are not otherwise subject of FIFRA review are encouraged to keep the Agency apprised of their activities. In addition, registrants of microbial pesticides are reminded that, pursuant to FIFRA section 6(a)(2), they must report any information regarding unreasonable adverse effects of the pesticide on the environment.

C. Microbial Pesticides—History and Long-Term Regulatory Strategy

1. *History.* Microbial pesticides have been in use for many years. In 1948, the Federal Government registered the first such product, *Bacillus popilliae*, to control Japanese beetle larvae in turf. However, it was not until the late 1960s and early 1970s that interest in microbial pesticides began to increase. At that time, EPA began to develop policies and procedures to specifically address microbial pesticide products. In 1983, EPA's Office of Pesticide Programs issued testing guidelines for microbial pesticides (Ref. 20). A year later, EPA issued a final regulation (40 CFR Part 158) specifying the data requirements for pesticide registration (including genetically engineered microbial pesticides). As of 1985, there were 14 microbial pesticides used in several hundred separate products registered for use in agriculture, forestry, mosquito control, and homes.

As indicated in Unit II.A above, EPA issued an interim policy on small-scale field testing of genetically altered and nonindigenous microbial pesticides in October 1984 (49 FR 40659). To date, under this policy, EPA has received and reviewed five notifications for genetically engineered microbial pesticides and two notifications for nonindigenous microbial pesticides. Three EUP applications, required in part to address unresolved issues identified in the review of these notifications, have since been received. These applications were for genetically engineered microbial pesticides.

2. *Lang-term regulatory strategy.* Although EPA has an established regulatory mechanism for microbial pesticides, the Agency envisions some further modifications in the future to specify certain policies in more detail, keep the assessment process current with existing scientific knowledge, and ensure an efficient review mechanism. Some of these anticipated modifications are discussed here.

As noted in Unit I, EPA intends to revise the EUP regulations (40 CFR Part 172) to incorporate the concepts embodied in the interim policy on small-scale field testing. Specifically, Part 172 will be revised to specify more clearly which applicants must notify EPA before conducting small-scale field tests with microbial pesticides and the content of notification.

As noted in the overview to this EPA notice (Unit I.F), EPA is forming a Science Advisory Committee. The Scientific Advisory Panel, an advisory group mandated by FIFRA, will continue to serve in its advisory capacity on specific submissions under FIFRA, until the SAC is formed.

FIFRA requires EPA to review and periodically update its guidelines, and OPP has begun this process for the Subdivision M Pesticide Assessment Guidelines. The Guidelines are currently being revised to reflect current testing methodology and advances in risk assessment capabilities resulting from OPP's recent experience in evaluating genetically engineered microbial pesticides. In addition, as the Agency gains risk assessment experience and assembles a larger body of risk assessment data, it may be appropriate to amend the Part 158 data requirements regulation to add to or modify the data requirements that apply to genetically engineered and nonindigenous microbial pesticides.

D. Regulatory Review of Microbial Pesticides

This unit describes EPA's data requirements and review procedures for microbial pesticides. In particular, Unit II.D.1 describes the requirements and review plan for those microbial pesticides subject to review under FIFRA before they may be used in any application in the environment (i.e., small-scale field testing). Unit II.D.2 outlines the regulatory review for those microbial pesticides subject to the FIFRA requirements for an experimental use permit or registration. In most instances, microbial pesticides subject to the provisions in Unit II.D.1 will also be subject to the provisions in Unit II.D.2 when they are to be used for larger scale or commercial purposes in the environment.

1. *Small-scale field testing.* Prior to obtaining a registration for a pesticide product, applicants generally need to conduct field studies in order to gather product performance, use, and other types of data necessary to support the registration of their product. The regulations governing field studies (40 CFR Part 172) include a generally applicable presumption that EUPs will not be required for certain small-scale uses of new pesticides (or new uses of previously registered pesticides). The Agency issued a statement of interim policy addressing small-scale field testing of microbial pesticides in 1984. The interim policy announced that the Agency should be notified before initiation of any field testing of genetically altered or nonindigenous microbial pesticides. The purpose of this policy is to provide a mechanism for the Agency to evaluate these proposed small-scale field tests for possible risk to human health or the environment and determine whether EUPs are required before the tests can be initiated.

Small-scale field studies are (1) terrestrial field studies that involve 10 acres or less of land; and (2) aquatic field studies that involve 1 surface acre or less of water.

To minimize the regulatory burden on producers of genetically engineered and nonindigenous microbial pesticides, and more closely correlate the level of Agency review with potential risk of the

microorganism, the Agency has adopted a two-level review system based on its evaluation of the potential risks posed by various types of microorganisms. The two-level system will allow the Agency to receive some basic information on small-scale testing of genetically engineered and nonindigenous microorganisms that are less likely to pose significant risks to humans or the environment (Level I reporting), while reserving full notification and review procedures for microorganisms about which there is more concern (Level II notification). The review system is designed so that producers of microbial pesticides may proceed with their small-scale field tests without Agency approval, unless they are notified within a specified time that additional information or an EUP is required. In the case of level I reporting, producers need only provide a limited amount of information, and are assured of an expedited response from the Agency if it is determined that additional information is required.

The two-level system is based on the analysis set forth at Unit I.D, in which the Agency has defined groups of microorganisms that raise more concerns about their likelihood to pose risks to humans or the environment, when released into the environment, than other microorganisms. Specifically, these include microbial pesticides formed by deliberately combining genetic material from organisms of different genera and genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms. However, other genetically engineered and nonindigenous microbial pesticides are less likely to pose significant risks to humans or the environment when applied in small-scale field test. Accordingly, the Agency has determined that this second category of microbial pesticides will be subjected to a reporting requirement and will be reviewed as described in Unit II.D.1 a through c below. The Agency will have up to 30 days to review the reported information. The kind of information needed to fulfill the reporting requirement is typically already available to an applicant as an essential part of product research and development, and is not generally expected to require generation of new data.

All microbial pesticides formed by deliberately combining genetic material from organisms of different genera, and all genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms will be subject to the full notification requirements (Level II) as described in Unit II.D.1.e below. The Agency has determined that these organisms should continue to be subjected to the full notification and review procedures set out in the original interim policy published on October 17, 1984. The Agency will have up to 90 days to review a Level II notification.

The scope and requirements for Level I reporting and Level II notification are detailed below. The interim policy as revised by this notice does not apply to studies conducted under enclosed, contained conditions, as defined in Unit IV.

a. *Level I reporting.* Level I reporting for small-scale field testing applies to all genetically engineered or nonindigenous microbial pesticides not otherwise covered by Level II notification as detailed in II.D.1.d below. Small-scale field tests of additional groups of genetically engineered and nonindigenous microbial pesticides now covered by Level II notification may also be determined to warrant only abbreviated review in the future. The Agency will make these determinations on a case-by-case basis.

b. *Level I information.* Each report should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Identity of the microorganism, including characteristics, and means and limits of detection.

(2) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(3) Information on the host range of the parental strain(s) or nonindigenous microorganism.

(4) Information on the relative environmental competitiveness of the microorganism, if available.

(5) If the microorganism is genetically engineered, information should be provided on the methods used to genetically engineer the microorganism(s); the identity and location of the rearranged or inserted/deleted gene segment(s) in question; a description of the new trait(s) or characteristic(s) that are expressed; information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

(6) A description of the proposed testing program, including site location, crop to be treated, target pest, amount of test material to be applied, and method of application.

c. *Level I reporting process.* EPA will have up to 30 days to review the above information to make a preliminary determination of the need for an EUP. If the Agency does not notify the applicant of the need for an EUP within the 30 days, the applicant may proceed with the proposed field test. If, on preliminary assessment, the test raises sufficient concerns such that the Agency determines that additional information or monitoring is warranted, then an EUP will be required (e.g., microorganisms for which there is limited scientific information or regulatory experience, or that raise significant questions concerning genetic stability, competitiveness, or mode of action, or that warrant specific environmental monitoring during the test). In this case, the applicant has two options. First, the applicant may apply for a permit, providing the necessary data and information required to support the application. Alternatively, the applicant may provide all additional data and information required under Level II notification as outlined in Unit II.D.1.e below. If the latter option is chosen, the Agency will have an additional 60 days to review the full notification package and make a final determination as to whether an EUP is required.

d. *Level II notification.* Level II notification for small-scale field testing applies to microbial pesticides: Microbial pesticides formed by deliberately combining genetic material from organisms of different genera, genetically engineered microbial pesticides derived from source organisms that are pathogens (as defined in Unit IV), and nonindigenous pathogenic microbial pesticides (as defined in Unit IV).

e. *Level II requirements.* Notification should include adequate information to allow the Agency to evaluate the small-scale field testing program. Each notification should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Background information on the microorganism.

(a) Identity of the microorganism, including tables of characteristics, and means and limit of detection using the most sensitive and specific methods available.

(b) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(c) Information on host range, especially infectivity and pathogenicity to nontarget organisms.

(d) Information on survival and ability of the microorganism to increase in numbers (biomass) in the environment (e.g., laboratory or containment facility test data).

(e) If the microorganism is genetically altered, the following information should be provided in addition to the information listed in (a) through (d) above:

i. Information on the methods used to genetically alter the microorganism.

ii. The identity and location of the rearranged or inserted/deleted gene segment(s) in question (host source, nature, base sequence data, or restriction enzyme map of the gene(s)).

iii. Information on the control region of the gene(s), and a description of the new trait(s) or characteristic(s) that are expressed.

iv. Information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

v. Information on relative environmental competitiveness compared to the parental strains.

(2) Description of proposed field test.

(a) The purpose or objectives of the proposed testing.

(b) A detailed description of the proposed testing program, including test parameters.

(c) A designation of the pest organism(s) involved (common and scientific names).

(d) A statement of composition for the formulation to be tested, giving the name and percentage by weight of each ingredient, active and inert, production methods, contamination with extraneous microorganisms, potency and amount of any toxins present, and where applicable the number of viable microorganisms per unit weight or volume of the product (or other appropriate system for designating the quantity of active ingredient).

(e) The amount of pesticide product proposed for use and the method of application.

(f) The State(s) in which the proposed program will be conducted, and specific identification of the exact location of the test site(s) (including proximity to residences and human activities, surface water, etc.).

(g) The crops, fauna, flora, geographical description of sites, modes, dosage rates, frequency, and situation of application on or in which the pesticide is to be used.

(h) A comparison of the natural habitat of the microorganism with the proposed test site.

(i) The number of acres, number of structural sites, or number of animals/plants, by State, to be treated or included in the area of experimental use, and the procedures to be used to protect the test area from intrusion by unauthorized individuals.

(j) The proposed dates or period(s) during which the testing program is to be conducted, and the manner in which supervision of the program will be accomplished.

(k) A description of procedures for monitoring the microorganism within and adjacent to the test site during the field test.

(l) The method of disposal or sanitation of plants, animals, soils, etc., that were exposed during or after the field test.

(m) Means of evaluating potential adverse effects and methods of controlling the microorganism if detected beyond the test area.

In addition, the following references should be consulted for further guidance on the kinds of data and information that may be relevant to the evaluation of genetically engineered microorganisms: "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11); "Subdivision M: Biorational Pesticides" (Ref. 20); a report by the Cornell Ecosystems Research Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs" (Ref. 9); a National Science Foundation Report titled "The Suitability for Environmental Applications of Biotechnology" (Ref. 3); and EPA "Points to Consider in the Microorganisms" (available from TSCA Assistance Office at the address given at the beginning of this notice).

f. *Level II review process.* Once the supporting data have been submitted, EPA has up to 90 days to review each notification of intent to conduct small-scale field testing and to determine whether an EUP is required. The Agency encourages prospective applicants to meet with EPA prior to submission of their notification to discuss their field test and determine what specific data would be necessary to evalaute the product.

EPA's review process will include some or all of the elements described in the following paragraphs. As the Agency builds a baseline of risk assessment data and gains more experience in evaluating these products, certain steps may no longer be necessary. In addition, an abbreviated review process may be appropriate in some situations (e.g., review of a proposal that is similar to an already reviewed case). Such a determination will be made on a case-by-case basis.

Once a notification is received, OPP reviews each proposal and assesses potential risks associated with the proposed experiment. OPP develops a written scientific position for each proposal which identifies potential problems or significant unanswered questions and sets forth a statement of the overall likelihood of significant risk from the proposed field testing. As the review process proceeds, it may be necessary for OPP to request supplemental information.

OPP obtains comments on its assessment from a workgroup within EPA and from other Federal agencies as appropriate (e.g., USDA, National Institutes of Health, Food and Drug Administration, and National Science Foundation). Their comments are incorporated into the scientific position, as appropriate.

OPP contacts the appropriate State pesticides regulatory authorities to ensure that they are aware of the proposal and to discuss EPA's assessment. These contacts ensure that the actions of EPA and the State agencies are as consistent as possible. OPP also notifies the Animal and Plant Health Inspection Service (APHIS) of the USDA so that they can determine whether any aspect of the proposed experiment falls within APHIS jurisdiction and, if so, to avoid duplicative or conflicting assessments.

Thus far, reviews of small-scale field testing proposals for genetically engineered microbial pesticides have emphasized some questions that have not been as significant in the assessments of naturally occurring microbial pesticides. For example, OPP has identified potential risks associated with the transfer of inserted genetic material to other organisms, the competitiveness of the engineered organism compared with the parental organisms in the environment, and the ability of the engineered organism to become established in a new ecological niche and thereby pose a potential adverse environmental impact.

OPP has addressed these and similar questions on a case-by-case basis in its risk assessments. In some cases, applicants have addressed questions by redesigning the proposed application or test microorganism to minimize the potential risk. In other instances, EPA has established data requirements and test methods as a baseline, and has designed specific laboratory test(s) (or

tiered series of tests) to establish whether the effect of concern is likely to materialize under field conditions.

If the notification raises complex or controversial scientific questions, OPP provides the notification package and its scientific evaluation to a group of independent scientists constituted as a subpanel of FIFRA's Scientific Advisory Panel. Separate subpanels may be formed to review each proposal since each microorganism and its proposed use may differ and raise questions that require the analysis of individuals with different expertise. The purpose of the SAP subpanel is to obtain an independent peer review of the OPP scientific position, to address specific scientific questions raised by OPP, and to identify any additional points, questions, or problems. As noted previously in Unit I.F, the Agency is forming a Science Advisory Committee which will assume these responsibilities in the future.

At the conclusion of the review, the Agency then decides whether an EUP is required. The decision document sets forth OPP's conclusions with respect to potential risks associated with the proposal, identifies any remaining questions or additional data that may be needed to complete the risk assessment, and, if an EUP is required, may recommend restrictions, limitations, or modifications of the proposal to address areas of concern. If an EUP is not required, the applicant may proceed with the proposed field test. If an EUP is required, the applicant must apply for a permit, providing the necessary data and information required to support the application. The Agency may decide to require an EUP to ensure that the experiment is conducted within certain defined limitations, the necessary data are developed to assess the proposal, or certain kinds of data are developed during the test and reported to the Agency.

2. *EUPs, large-scale testing, and registration.* Before a pesticide may be marketed as a commercial product, it must first be registered as provided for in section 3 of FIFRA. Large-scale field testing of a microbial pesticide is often necessary to evaluate a potential product and obtain data needed to support registration of the product. This testing, like small-scale field testing under an EUP, is subject to section 5 of FIFRA which authorizes EPA to approve applications for EUPs for limited use of an unregistered product or use of a registered product for an unregistered use. Data requirements for registration are specified in 40 CFR 158.170 and a subset of these requirements applies to large-scale field testing proposals to be performed under EUPs. The regulatory review process consists of the same basic elements in both situations and is described in this unit.

a. *Scope.* All microbial pesticides to be used in large-scale field tests are subject to review under FIFRA EUP regulations. The conditions under which an EUP is required are specified at 40 CFR Part 172, which also provides guidance on how to determine whether an EUP must be obtained. Likewise, all microbial pesticides are subject to the FIFRA registration requirements.

b. *General requirements for microbial pesticides.* The existing pesticide data requirements and regulations governing large-scale field testing (40 CFR Parts 158 and 172) and registration (40 CFR Parts 158 and 162) are applicable to all microbial pesticides, both naturally occurring and otherwise.

The agency believes that these requirements are adequate for the assessment of indigenous microbial pesticides, and provide a basis for evaluating genetically engineered and nonindigenous microbial pesticides as well. However, the Agency believes that additional data and information, determined on a case-by-case basis, may be necessary to evaluate some properties of genetically engineered and nonindigenous microbial pesticides. Part 158 explicitly provides the necessary flexibility to require additional data (§ 158.65) as well as the flexibility to waive data requirements that are not applicable (§ 158.45).

c. *Additional requirements for genetically engineered and nonindigenous microbial pesticides.* Any additional data requirements will be determined on a case-by-case basis depending on the particular microorganism, its parent microorganisms, its native habitat, the pesticide use pattern, and the manner and extent to which the microorganism may have been engineered. These additional requirements could include:

(1) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(2) Information on relative ability to survive and increase in number or biomass as compared to the parental strains.

(3) Selected environmental fate tests from 40 CFR 158.170.

(4) Additional toxicology tests from 40 CFR 158.170.

(5) If the microorganism is genetically altered, then information on the genetic modification techniques used, the identity of inserted gene segment(s) (base sequence data or restriction enzyme map of the gene), the control region of the gene(s), a description of the new traits or characteristics that are intended to be expressed, and tests to evaluate genetic stability and exchange, may be required as specified previously at Unit II.D.1.b above.

d. *Review process for genetically engineered and nonindigenous microbial pesticides.* EUP applications will be reviewed in compliance with the EUP regulations under 40 CFR Part 172. The registration, reregistration, and classification procedures of 40 CFR Part 162 will be followed for registration applications. The review process will contain the same major elements as those outlined previously for small-scale field testing notifications (see Unit II.D.1.c). Briefly, this process involves scientific review and risk assessment by EPA scientists and, if appropriate, review and comment from other Federal agencies and independent expert consultants.

Once the supporting data have been submitted, EPA has up to 120 days to review an EUP application and determine whether to grant a permit. Past experience indicates that the registration process for a new microbial pesticide may vary from 9 months to several years depending upon the particular product, its use pattern, and the completeness of the registration package submitted to EPA.

Both the EUP and registration process may provide an opportunity for public comment. For example, § 172.11 of the EUP regulations specifies that if an application may be of regional or national significance the Agency will announce receipt of the application in the **Federal Register.** The announcement is accompanied by a description of the experimental program and public comments are solicited. Similarly, § 162.6 of the registration regulations specifies that if a registration application relates to a new active ingredient or a new use, notice of receipt of that application shall be published in the **Federal Register** with a request for public comment. Information on the submission is made available for public inspection.

EPA has several regulatory options for responding to either an EUP or registration application. For example, after completing its review, the Agency may determine that the field test or registration poses no unreasonable risks to humans or the environment and may grant the application. Alternatively, EPA may conclude that some additional information or data are needed to assess the potential risks adequately. In this

case, the application would be asked to provide the necessary data before EPA would decide whether to grant the application. In other cases, the Agency may impose additional limitations or restrictions on the field test or registration to address a potential risk. Finally, EPA will deny those applications where it has determined that it has all the necessary data to complete a risk assessment and that the field test or registration would pose an unreasonable risk to humans or the environment, even if additional limits or restrictions are imposed.

III. Applicability of the Toxic Substances Control Act (TSCA) to Microbial Products

A. Overview of This Unit

As discussed in the December 84 notice (49 FR 50886), EPA will review certain microorganisms and uses of microorganisms under TSCA. Microorganisms and their DNA molecules are "chemical substances" under section 3 of TSCA, and thus are subject to all the provisions of TSCA, except to the extent they are manufactured, processed, or distributed in commerce for use as pesticides, foods, food additives, drugs, cosmetics, and medical devices. For purposes of analysis and convenience of administering TSCA, EPA has chosen to focus on the microorganism as the "chemical substance."

This unit explains the statutory requirements of TSCA as they apply to microorganisms. It begins by describing which microorganisms are within the scope of TSCA and which are not. Following that are units describing five categories of microorganisms or uses of microorganisms that are or will be subject to reporting requirements under TSCA.

B. Scope of TSCA

Many organisms are not subject to TSCA requirements because of statutory exemptions; others will be exempt from certain TSCA requirements as a matter of regulatory policy. In general, the use of a microorganism determines whether it is subject to TSCA or to other laws.

Many of the comments received by OTS indicated misunderstandings of TSCA's scope. Therefore, those organisms which are and are not subject to TSCA are described in this Unit.

1. *Organisms not subject to TSCA*—a. *Microbes used as foods, food additives, drugs, cosmetics, medical devices, and pesticides.* Microorganisms are sometimes used directly as foods, food additives, drugs (including both human and animal vaccines), cosmetics, medical devices, and pesticides. When microorganisms are used for these purposes, they are explicitly excluded from TSCA and from the policies described in the TSCA portions of this notice (TSCA section 3(2)(B), 15 U.S.C. 2602(2)(B)).

Microorganisms that are used as foods, food additives, drugs, cosmetics, medical devices, and pesticides are regulated by the Food and Drug Administration (FDA), USDA, or the EPA Office of Pesticide Programs. Applicable requirements for pesticides are described in Unit II of this notice. Requirements for foods, food additives, drugs, cosmetics, and medical devices are described in the FDA and USDA notices in this **Federal Register**.

b. *Microbes used to produce foods, food additives, drugs, cosmetics, and medical devices.* In addition to being used themselves for food, drug, and other purposes, microorganisms are often used to produce chemicals that are in turn used for such purposes. For reasons explained in the December 84 notice, microorganisms will not be reviewed under TSCA when used to produce foods, food additives, drugs (including vaccines), cosmetics, or medical devices. Further information on these uses may be found in the FDA and USDA notices in this **Federal Register**.

Microorganisms used in the production of chemical end products other than foods, food additives, drugs (including vaccines), cosmetics, and medical devices are subject to TSCA. They are described in Unit III.B.3 below.

2. *Plants and animals not subject to these policies.* Plants and animals are not subject to the TSCA policies in this notice, either as whole organisms or as *in vitro* cultures for the reasons set forth in the December 84 Notice. (Definitions of plants and animals for regulatory purposes are provided in Unit IV of this EPA notice.) There are two exceptions to this general rule. First, if plant or animal gene segments are intentionally incorporated into microorganisms, the microorganisms that contain those plant or animal genes may be subject to TSCA, depending on how they are used (see Units III.B. 1 and 3). Second, a chemical extracted from a plant or animal may be subject to TSCA, again depending on how it is used. The USDA and FDA notices in this **Federal Register** contain information about regulations that apply to plants and animals.

3. *Organisms subject to TSCA—microorganisms used for purposes not excluded by law.* With the exceptions described above, all microorganisms produced for environmental, industrial, or consumer uses are potentially regulable under TSCA. It is not possible to list all the applications that could be subject to TSCA because many are yet to be developed. Some of the microorganisms that are expected in the near future and that would be subject to TSCA include microorganisms used in conversion of biomass for energy, pollutant degradation, enhanced oil recovery, metal extraction and concentration, and certain non-food and non-pesticidal agricultural applications, such as nitrogen fixation.

Microorganisms used in the production of a chemical end product will be subject to TSCA if the end product is any chemical substance used for a purpose other than as a food, food additive, drug, cosmetic, or medical device. For example, microorganisms are subject to TSCA if they are used in the production of pesticides, fuels, solvents, dyes, cleansing agents, etc. TSCA jurisdiction over such microorganisms, which may be used entirely in closed manufacturing systems, is consistent with TSCA coverage of conventional chemicals. For example, chemical intermediates—even those used in closed systems—fall under TSCA authority and are subject to PMN requirements if new (40 CFR Part 720). Similarly, as described in Unit III.C.1 of this notice, "new" microorganisms used in chemical production are subject to PMN requirements.

4. *Chemicals produced by microorganisms—Status under TSCA.* Although the purpose of this notice is to provide information on the applicability of TSCA to microorganisms, some readers may wish to obtain information on requirements that apply to chemicals produced by microorganisms. For example, various proteins and polysaccharide gums are produced by microorganisms and may be subject to TSCA, depending on how they are used (see Unit III.B.1). These chemicals produced by microorganisms are subject to the same requirements and procedures as chemicals produced by other means. Any special concerns pertaining to the microbial production method, such as the possibility of contaminants, will be considered during the review of the microorganisms used in producing the chemicals. This approach is explained in the December 84 notice at page 50890.

C. Specific Requirements Under TSCA

The fact that a microorganism is potentially subject to TSCA does not necessarily mean that it will be regulated under TSCA. The rest of this unit explains the specific provisions that apply or will apply to various types of

microorganisms falling within TSCA's jurisdiction.

In overview, microorganisms are (or will be) subject to TSCA requirements in the following manner:

As of the date of this notice, microorganisms that are subject to TSCA and contain genetic material from dissimilar source organisms (i.e., organisms from different genera) are subject to PMN requirements.

Microorganisms other than inter-generic combinations that are subject to TSCA and are pathogenic or contain genetic material from pathogens, will in the future, if released into the environment, be subject to "significant new use" reporting requirements under TSCA section 5(a)(2). One exception is that agricultural uses of such microorganisms will be reviewed by USDA rather than EPA. EPA expects voluntary notification to begin immediately for uses that will be subject to significant new use reporting requirements.

The research and development exemption from PMN and significant new use notification requirements will be amended so that it no longer applies to microorganisms released to the environment. EPA expects voluntary notification of such uses to begin immediately.

EPA will issue a rule requiring manufacturers and importers to submit general information on environmental uses of microorganisms that are subject to TSCA but not otherwise subject to notification requirements, so that EPA can monitor environmental releases.

All manufacturers, processors, and distributors of microorganisms subject to TSCA are reminded of the requirement to report any information on substantial risks under TSCA section 8(e).

EPA is considering initiating rulemaking that would exempt from PMN requirements inter-generic microorganisms used solely in contained systems and never intentionally released to the environment.

1. *Premonufacture notification requirements*—a. *Overview.* EPA has determined that any microorganisms that are subject to TSCA (described in Unit III.B), and that through deliberate human intervention contain genetic material from dissimilar source organisms, are "new" and therefore subject to PMN requirements of TSCA. This interpretation is effective as of the date of publication of this notice.

Organisms are considered dissimilar for the purposes of this policy if they are from different genera. In the case of chemically synthesized genes, the Agency will follow the same principle, as clarified below in Unit IV. Detailed guidance on how to determine if organisms are from different genera is also provided in Unit IV.

The agency is excluding certain inter-generic combinations from PMN requirements, i.e., those inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions (see Unit IV). The resulting microorganisms do not possess new combinations of traits but rather exhibit quantitative changes in preexisting traits.

EPA is leaving unanswered, for now, the question of whether microorganisms containing genetic material from other microorganisms in the same genus (i.e., products of deliberate intra-generic combinations) and those which are developed from a single source microorganism (e.g., products of undirected mutagenesis, microorganisms with deletions) should also be considered "new." In the future, it is possible that EPA will decide that such microorganisms are "new," but for now they are not subject to PMN requirements.

b. *Background.* For purposes of administering TSCA, EPA must decide what constitutes a "new" microorganism which is subject to PMN requirements. As mentioned in the introduction to the EPA portion of this notice, EPA originally proposed a "process-based" approach to determining whether a microorganism is new. This approach stated that a microorganism would be considered new if significant human intervention had been used in developing it. For example, microorganisms altered by certain techniques—such as recombinant DNA and cell fusion—were presumed to be new because they involved significant human intervention. The question of which other techniques should be considered to produced new microorganisms was left open and comments were solicited.

After reviewing the comments, EPA considered a number of alternative ways to define "new" microorganisms. These are described in the "Response to Comments" document available as background to this Federal Register notice. In choosing among the alternatives, EPA carefully considered the TSCA mandate to review "new" substances. The Agency also considered related issues, for example, how well the options approximated risk (there was uncertainty with all the options in this respect) and how readily they could be implemented and enforced.

c. *Rationale.* Having reviewed the TSCA section 5 PMN requirements, the PMN regulations, the public comments, and the current state of science regarding genetic engineering, EPA has concluded that microorganisms resulting from intentional, inter-generic combinations of genetic material, except those in which the transferred material is only a well-characterized, non-coding regulatory region, constitute new microorganisms for purposes of PMN reporting. The reasons for this are set forth below.

First, the Agency considered the regulatory precedents established in compiling the inventory of existing chemical substances under section 8(b) of TSCA. Any chemical substance not on this inventory is "new" under section 5(a) of TSCA and is therefore subject to PMN requirements. Naturally occurring substances and substances derived from nature with limited human intervention are not explicitly listed on the inventory but are considered implicitly to be on it, and thus are not "new" (see 40 CFR 710.4(b)). A more detailed explanation of the TSCA inventory and related issues is found in the December 84 notice at pages 50887–50888.

Second, the Agency evaluated these regulatory precedents in the light of scientific knowledge about genetic engineering and microorganisms found in nature. On this basis, EPA concluded that microorganisms found in nature and developed without any deliberate combination of genetic material are not new, because they occur naturally and are derived through limited human intervention. Furthermore, from a scientific standpoint, these microorganisms have a very low probability of exhibiting new combinations of traits. Therefore, the Agency considers that from a legal and scientific standpoint they must be considered naturally occurring (not new). Because such microorganisms are naturally occurring, they are, as explained above, implicitly listed on the TSCA chemical substances inventory and not subject to PMN requirements.

Third, where genetic material has been combined among source organisms from different genera (inter-generic), the resulting microorganisms should be considered "new" because of the degree of human intervention involved, the significant likelihood of creating new combinations of traits, and the greater uncertainty regarding the potential risks of such microorganisms. However, transfer of genetic material consisting solely of well-characterized, non-coding regulatory regions is a special case. Where only regulatory material is

transferred, no distinctly new combinations of traits are introduced; instead, existing traits in the receiving microorganisms are amplified or changed quantitatively. For this reason, EPA believes that microorganisms formed only through inter-generic transfer of well-characterized, non-coding regulatory regions should not be considered "new" under section 5 of TSCA. This is reflected in the definition of "inter-generic" found in Unit IV.A.

It is possible to argue that some microorganisms formed through intra-generic combinations are products of significant human intervention and may exhibit new combinations of traits, and therefore that they should also be considered new. However, the Agency at this time believes that it is appropriate to exclude such microorganisms form its definition of "new" because distinctly new combinations of traits are unlikely to occur through transfers of genetic material among closely related organisms, because transfers among closely related organisms are more likely to occur in nature, and because the current state of taxonomy with regard to species designations is sufficiently unstable that it makes it difficult to include such microorganisms in a definition of "new" (the rationale is found in Unit I.D.3.a). As explained previously, however, the Agency will continue to review the status of such microorganisms and may, in the future, determine that certain combinations among similar organisms should be considered new.

In summary, EPA considers microorganisms deliberately formed to contain genetic material from different genera to be new, except where only well-characterized, non-coding regulatory regions are transferred. Conversely, intra-generic and non-engineered microbes are considered naturally occurring. These conclusions are based on the TSCA section 5 mandate to review "new" substances, and they also reflect a number of scientific considerations. Among these are (1) the Agency's concern that microorganisms formed with genetic material from different genera warrant regulatory review, because of the inherent uncertainty about the characteristics and behavior of such microorganisms, (2) the observation that microorganisms from different genera are less likely to exchange genetic material in nature than microorganisms that are more closely related, (3) the regulatory precedent that significant human intervention creates new substances for purposes of PMN under TSCA section 5, and (4) the necessity of having a definition of "new" that can be readily interpreted and enforced given the current state of science. These scientific and legal issues are more fully described in Unit IV.A.

d. *How to comply with the PMN requirements for new microorganisms.* The following requirements apply to "new" microorganisms produced for uses subject to TSCA authority (see Unit III.B.1 and 3). Detailed criteria for determining whether a microbe meets the definition of "new" microorganism (i.e., whether it contains genetic material from organisms from different genera) may be found in Unit IV.A.

Certain PMN policies in this notice are immediately effective. As of the date of publication of this notice, microorganisms that are being manufactured or imported for any TSCA commercial purposes other than research and development (R&D) are subject to PMN requirements 90 days prior to manufacture or import. This requirement applies to both contained and environmental uses that have gone beyond R&D. The requirement is based on the current provisions of 40 CFR Part 720. The definition of R&D under these regulations is clarified in the Federal Register of April 22, 1986 (51 FR 15096).

In addition, new microorganisms that are being manufactured or imported for R&D that involves environmental release will have to be reported to EPA at least 90 days before such activities begin. This policy will be implemented through amendments to 40 CFR 720 (explained fully in Unit III.C.3); in the meantime, persons manufacturing or importing new microorganisms for R&D activities involving environmental release are expected to comply with this policy voluntarily.

EPA believes that there are no manufacturers who are presently beyond the research and development stage with new microorganisms subject to TSCA. However, if any companies are now engaged in such activities, they should contact EPA and determine whether a PMN is necessary. If a company in this position contacts EPA promptly, it will not be considered out of compliance with policy. Further information on TSCA PMN requirements may be obtained from the TSCA Assistance Office (address provided at the beginning of the EPA portion of this notice).

(1) *How to know if a microorganism is subject to PMN.* As stated above, all microorganisms containing deliberate combinations of genetic material from organisms from different genera are new and subject to PMN. An exception to this policy is an inter-generic combination in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. Unit IV.A of this notice contains detailed guidance that manufacturers should use to determine if their microorganisms meet this definition.

Submitters should consult the Agency if they have any questions about how to determine if a microorganism contains genetic material from different genera.

(2) *PMN exemptions.* EPA considers it a priority to exempt from PMN requirements new microorganisms that can be shown to meet the findings for exemption under TSCA section 5(h)(4). Further information on exemptions the Agency is considering may be found in Unit III.C.6 of this notice.

(3) *Submitting the PMN.* EPA expects manufacturers and importers to contact EPA well in advance of PMN submission, to allow sufficient time for prenotice consultation. These consultations will help the Agency and the submitter anticipate potential problems and expedite the review.

Information regarding new microorganisms should not be submitted on the standard PMN form, as this form is not applicable to microbial products. Instead, EPA and the submitter will discuss the level and types of information appropriate for the notice during prenotice consultations. The general kinds of information EPA expects to see in most submissions for microorganisms are described in the next unit below.

(4) *What information to submit.* Section 5(d)(1)(A) of TSCA specifies the information PMN submitters must provide in their notices, including information on production, workplace exposure, and release. In addition, under section 5(d)(1)(B) submitters must provide all test data related to the health and environmental effects of the new chemical substance in their possession or control. For more information on PMN requirements, persons should consult EPA's PMN rule (40 CFR Part 720).

In general, information to assess a substance's potential risk should be developed in a step-wise fashion. PMN submitters should begin with published literature on the source organisms, then move through laboratory, microcosm, growth chamber, and/or greenhouse studies that simulate as closely as possible the conditions of the eventual use or environmental application.

The remainder of this unit describes the types of information EPA expects

submitters to provide in PMNs on new microorganisms.

(a) *Identifying the microorganism.* PMN submitters must provide information that identifies microorganisms well enough to be listed on the TSCA chemical substance inventory. If the identity and/or use of the microorganism are claimed as confidential business information by the submitter, the PMN must also include a generic description of these items so that the information can be published in the Federal Register. Confidential submissions will be considered incomplete unless this generic information is included (see 40 CFR 720.65, 720.85, and 720.87).

Once a new microorganism is actually manufactured or imported, it will be listed on the inventory and will be no longer subject to PMN requirements. (See 40 CFR 720.102 concerning submission of a Notice of Commencement of Manufacture or Import.) EPA proposed an approach to inventory listings in a background document to the December 84 notice. The Agency received very few comments on this document, but those who commented stated that a general method for listing all microbes does not seem possible at this time. The Agency agrees and therefore intends to list microorganisms on the inventory on a case-by-case basis while developing more general procedures for different classes of microorganisms, and gaining experience that will help in developing standard listings. For now, the inventory definition will usually include the genus and species designations of source organisms and of the microorganism being reported, and other relevant phenotypic information such as nutritional and substrate requirements, proteins expressed, primary characteristics for which the microbe was engineered, and characteristics that are a typical for the species.

To identify the microorganism, EPA is likely to require information on:

i. Source organisms (e.g., taxonomy, source, reproductive cycle, and capacity for genetic transfer).

ii. Methods used to manipulate source organisms genetically to obtain the resulting product (e.g., source and function of genetic material to be combined; description of methods for vector construction and introduction, fusion of cells, injection of DNA, etc.).

iii. The special functions obtained (e.g., new traits intended to be expressed; selection method; nature and amount of source genetic material remaining in the product microorganism; genetic stability of new trait).

(b) *Risk assessment information.* Data required for conducting the risk assessment will vary according to the specifics of each case, but in general will fall into several major categories: Information on exposure, environmental fate, and human health and environmental effects.

If the microorganisms will be produced in enclosed, commercial-scale facilities, or used solely in physically contained systems, the notice should include the following information:

i. Production processes (e.g., culture conditions and requirements; sites, methods, and amounts of manufacture, processing, storage, and shipment; volume, composition, and disposal of wastes).

ii. Workplace exposure and worker practices (e.g., potential for exposure, worker protection practices, and equipment).

iii. Containment and possible releases (e.g., potential sources and characteristics of releases, physical containment methods, emergency back-up systems, monitoring, and detection methods in event of a release).

In the case of small-scale field tests and other environmental releases, EPA expects that the submitter will provide information on:

(A) Purpose and intended effect of application.

(B) Site of application and surroundings, including geographic, physical, chemical, and biological features.

(C) Numbers of microorganisms and methods of application.

(D) Containment and mitigation measures (e.g., procedures in event of accidental release, for emergency termination of the application, and to reduce dispersal beyond the site).

(E) Monitoring (e.g., detection procedures including their limits, sampling procedures).

For field tests and other environmental releases, data on environmental fate and effects will be essential. In such cases, manufacturers should assume, in the absence of data to the contrary, that the microorganisms may present a risk because of their potential to reproduce and exhibit new traits. Therefore, EPA will expect manufacturers to provide test and other data demonstrating the microorganisms' safety. These data should include:

(i) General background information on the source organism (e.g., habitat and geographic distribution, interactions with other organisms, involvement in biological cycling processes, potential for genetic exchange in nature).

(ii) Test data on the new microorganism itself, indicating its potential for survival, replication, dissemination, and genetic exchange with other organisms.

For further guidance, manufacturers should refer to the "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11). This document is particularly useful in developing data and information for submissions on small-scale field tests. While some points in this document relate solely to recombinant DNA techniques, most of the considerations are relevant to environmental tests of microorganisms regardless of the techniques involved in their production.

In addition, the Agency has prepared a more detailed guidance document entitled "Points to Consider in the Preparation and Submission of PMNs for Microorganisms." This document provides guidance on both environmental and industrial applications of microorganisms and is available from the TSCA Assistance Office (see address at the beginning of this notice).

At least three other documents will be useful to submitters. These are the "EPA Pesticide Assessment Guidelines: Subdivision M—Biorational Pesticides" (Ref. 20), a National Science Foundation report titled "The Suitability and Applicability of Risk Assessment Methods for Environmental Applications of Biotechnology" (Ref. 3), and a report by the Cornell Ecosystems Research Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs (Ref. 9).

e. *The PMN review.* All reviews of microorganisms will follow established administrative steps that are the same for all substances subject to PMN review. First, within 5 days of receiving the PMN, EPA will issue an announcement in the Federal Register describing the submission. The anouncement will include information on the identity of the new microorganism, the type of use, occupational exposure, production volume, a summary of test data submitted in the notice, and the submitter's identity. It will have confidential business information deleted according to the manufacturer's instructions, although EPA will strongly encourage manufacturers to release as much information as possible. If identity and use are claimed confidential, the Agency will include a generic description provided by the submitter.

EPA will have 90 days to review the PMN (extendable to 180 days), during which time the microorganism cannot be manufactured or processed for purposes other than research and development. Within the review period, the Agency may take action under section 5(e) of TSCA to prohibit or limit the activities, pending receipt of more data, or under section 5(f) or 6 to prohibit or limit the activities if there is sufficient information to make an unreasonable risk finding. Alternatively, EPA may take no action. In this case, manufacture and use may begin without restriction.

(1) *Case-by-case assessments.* Because of the very recent development of genetically engineered microorganisms for environmental use, there is little direct experience for conducting risk assessments on environmental releases of engineered microorganisms. In the absence of such experience, the Agency will conduct case-by-case reviews by using information from various scientific disciplines and by directly considering the features of specific genetically engineered microorganisms and their uses.

Many existing risk assessment approaches that are used for non-engineered microorganisms will contribute to the analysis of risks of engineered microbes in the environment. Some of these will be adopted with few if any changes, while others will require modifications to address special problems.

EPA believes that standardized protocols and procedures should be gradually blended with the case-by-case approach. As experience is gained, increasingly detailed guidance on routine testing and procedures can and will be developed.

(2) *Use of experts.* Expert judgment will be critical in determining information needs, evaluating protocols for testing, and reviewing potential risks. Because of the range of expertise that may be required in any given case, EPA intends to supplement its staff expertise by using experts from other government agencies, academia, and other independent sources. Persons will be specifically chosen for their knowledge and experience with organisms and uses related to the PMN under review.

As announced in the December 84 notice (and further described in Unit I of this notice), EPA is forming a biotechnology Science Advisory Committee to provide scientific advice and promote consistent review procedures.

Many academic experts may have financial or contractual relationships with biotechnology companies. Using non-Agency experts to assist in PMN reviews may therefore raise two potentially sensitive issues: Conflicts of interest and access by non-Agency experts to confidential business information. To address these issues, the EPA Office of Toxic Substances has developed special procedures to ensure that scientists contributing to biotechnology PMN reviews will not have conflicts of interest, and will have the necessary access to CBI to review the PMN without compromising trade secrets or violating TSCA CBI procedures. A document describing these procedures will be placed in the public record for this policy statement.

(3) *Major ports of the review process.* As stated earlier, EPA expects persons developing biotechnology products to engage in prenotice consultations with the Agency. During these discussions, EPA and the consulting company can identify preliminary concerns by considering the source organisms and intended uses of the microorganism subject to PMN. Significant time may be saved later in the PMN process if these concerns are addressed before the PMN is submitted.

Once the PMN is submitted, EPA will develop hazard and exposure assessments based on information submitted in the PMN, other available information, and consultation with non-Agency experts. Reviewers will consider the types of issues and questions described here and in the various guidance documents on risk assessments for microorganisms. As appropriate, they may also consult with external scientific experts, and their analyses may be peer reviewed by the Agency's biotechnology Science Advisory Committee.

As a risk/benefit statute, TSCA requires that benefits be estimated and considered in judging whether the risk may be unreasonable. While the risk assessments are being developed, Agency economists will estimate the benefits of the product based on information from the submitter, independent economic research, and consultation with non-Agency experts.

Finally, EPA staff will prepare a summary of the risks and benefits to use in reaching regulatory decisions.

(4) *Public involvement in the review.* EPA will issue for publication a section 5(d)(2) notice after receipt of a PMN for a new microorganism. EPA will also maintain a copy of the PMN, from which CBI has been deleted, in the OTS Public Information Office at the address listed in Unit VI of the EPA notice. EPA will welcome comments from interested members of the public on the PMN. The public is generally given 30 days to comment on a PMN after publication of the section 5(d)(2) notice.

In addition to the normal procedures for public comment on PMNs, EPA intends that meetings of its biotechnology Science Advisory Committee will be open to the public, although certain portions of meetings may have to be closed to discuss CBI. EPA also intends to charter its committee to include representatives from the lay public. These features will help to ensure that the public has access to information about EPA biotechnology policies and decisions.

(5) *Possible regulatory decisions.* The Agency may come to one of three decisions at the conclusion of a particular PMN review: (a) There is sufficient information to determine that the risks are reasonable, (b) there is sufficient information to determine that the risks are unreasonable, or (c) there is insufficient information to make a reasoned evaluation of risk, and the substance may present an unreasonable risk or there may be significant or substantial exposure to it.

Where the first decision is made, the Agency will notify the PMN submitter that the manufacture and use may proceed without restriction. In any event, unless the Agency notifies the company to the contrary before the end of the 90-day review period (with a possible 90-day extension), the submitter may begin to manufacture and use the organism.

A decision that risks will be unreasonable leads to two regulatory options. The Agency may require measures to reduce the risks to an acceptable level as a condition of manufacture and use. Alternatively, the Agency may prohibit manufacture or use of the microorganism if there are no alternatives available or practical to reduce the risk sufficiently. Such actions can be taken under TSCA section 5(f).

If the information submitted with the PMN is insufficient for a reasoned evaluation, and EPA finds that the microorganism may present an unreasonable risk or that there may be significant or substantial human exposure to it, or substantial environmental release, EPA may, under TSCA section 5(e), limit or prohibit the manufacture or use of the microorganism until sufficient data are submitted to the Agency to evaluate the risks.

2. *Significant new uses of microorganisms*—a. *Overview.* EPA intends to supplement its PMN requirements by requiring persons to notify the Agency before they introduce

pathogenic microorganisms (including microorganisms containing genetic material from pathogens) into the environment. Notification will be required for new environmental applications of genetically engineered pathogens prior to their release in any amounts into the environment, while notification for nonengineered pathogens will be required at a somewhat later stage, prior to their introduction on more than 10 acres of land (or some equivalent measurement standard in cases where acreage is not applicable, e.g. aquatic uses). If a pathogen used for agricultural purposes is subject to USDA review, it will not be subject to this policy. Applicable definitions may be found in Unit IV.

EPA intends to implement these notification requirements through a significant new use rule (SNUR) under TSCA section 5(a)(2). The public will have the opportunity to comment on the proposed rule, including its scope and possible categories that could be excluded from coverage.

Until the rule is final, EPA expects persons introducing pathogens into the environment for non-agricultural new uses to report to EPA voluntarily. In the unlikely event that an imminent hazard would arise during this interim period, the Agency could use its authority under section 7 of TSCA to immediately limit or prohibit the manufacture, processing, distribution in commerce, use, or disposal of the hazardous product.

b. *SNUR background.* Section 5(a)(2) of TSCA (15 U.S.C. 2604(a)(2)) authorizes EPA to determine that a use of a chemical substance is a significant new use. The Agency must make this determination by rule, after consideration of all relevant factors, including those listed in section 5(a)(2). Once EPA determines that a use of a chemical substance is a significant new use, section 5(a)(1)(B) of TSCA requires persons to submit a notice to EPA at least 90 days before they manufacture, import, or process the substance for that use.

Persons subject to a SNUR must comply with most of the same notice requirements and regulatory procedures as submitters of PMNs under section 5(a) of TSCA. EPA's review procedures and regulatory authority are the same for SNUR notices as for PMNs. However, if EPA does not take action on a SNUR notice, section 5(g) of TSCA requires the Agency to explain in the Federal Register its reasons for not taking action. Procedures and requirements for PMN review are described above in Unit III.C.1.

c. *SNUR rationale.* As explained in the December 84 notice, EPA recognizes that any approach to defining "new" microorganisms, including the one described in Unit III.C.1, excludes some types of microorganisms from PMN review and therefore may not address some significant potential risks. EPA believes there is one currently identifiable category of microorganisms that is not being treated as "new" under TSCA at this time but that should be reviewed before environmental release. That category includes pathogens and microorganisms that contain genetic material from pathogens (henceforth, both are referred to collectively as "pathogens"). As explained in more detail in Unit I, the Agency believes it is necessary to review pathogens released to the environment because of their ability to cause disease in microbes, plants, animals, and humans.

EPA intends to take a slightly different regulatory approach with nonengineered pathogens. The Agency will not require SNUR reporting on the use of nonengineered pathogens until they are to be used on more than 10 acres of land, or some equivalent standard (to be determined) for uses where acreage is an inappropriate standard (e.g. aquatic or subterranean uses). The reason for this exception is explained in Unit I.D., "Rationale for Approach."

To avoid duplicative requirements with USDA, EPA will exclude pathogens used solely for agricultural purposes from the scope of its SNUR. USDA permits to use such microorganisms are mandatory, while EPA review would be discretionary because these are not "new" microorganisms. However, new environmental applications of pathogens for non-agricultural purposes will be subject to EPA review as significant new uses, and will in some cases also be subject to USDA oversight (if they are plant or animal pests under the USDA definition). In such cases, USDA's review will primarily be for the purpose of detecting potential adverse agricultural effects, while EPA's review will focus on the potential non-agricultural impacts. See Unit I.E for an explanation of how the agencies will work together to coordinate their review.

EPA is considering whether it should also include provisions in the SNUR requiring notification prior to small-scale releases or commercial uses of other categories of microorganisms besides pathogens. For example, some people have expressed concern over nonindigenous microorganisms, and others have expressed concern over microorganisms that degrade structural components of nature such as lignin and cellulose. Members of neither category are subject to PMN when the microorganisms involved are naturally occurring or intra-generic (not new), and they would not be subject to the provisions for pathogens described above. However, they may present certain risks because they are new to the environment in which they are used or because of their degradative capabilities. The literature contains much documentation of the adverse effects that have occasionally been caused by nonindigenous microorganisms such as the chestnut blight fungus and Dutch Elm disease fungus. There is, on the other hand, very little known about many degradative microorganisms and their potential for adverse effects. The Agency will request comments on these concerns when it issues its proposed SNUR.

d. *Guidelines for voluntary compliance.* The SNUR that EPA will propose will describe, in detail, the persons who will be subject to the rule and the microorganisms and activities for which significant new use reporting will be required. In the meantime, EPA strongly encourages persons who are planning to manufacture, import, or process pathogenic microorganisms for non-agricultural, new environmental uses, except those used solely for agricultural purposes, to report their activities to the Agency and to provide information similar to that required for a PMN for a new microorganism.

For purposes of voluntary reporting, persons may use the following definitions and assumptions. These guidelines may be changed in the proposed and final forms of the SNUR.

(1) *How to know if a use would be considered a significant new use.* For purposes of voluntary reporting, the Agency encourages people to be as comprehensive as possible and to consider that any new, non-agricultural release of a pathogen to the environment is appropriate to report. "Environmental release" is defined in Unit IV.D, this definition should be used in the interim until the SNUR is final. Cases that may not be entirely clear, e.g., use in waste water treatment plants and use in mines or oil wells, should be reported until the Agency provides further guidance.

Many microorganisms that are pathogens or that contain genetic material from pathogens are being used in the environment already. For example, specific naturally occurring pathogens are used for waste treatment purposes and are tested in non-contained experiments. These applications of these specific microorganisms cannot be considered

significant "new" uses because they are ongoing. Therefore, persons now using pathogens in environmental applications will not be expected to notify the Agency of such uses of these pathogens, except for informational purposes (see Unit III.C.4).

In developing the proposed and final rule, the Agency will have to determine exactly which types of uses should be considered significant new uses, taking into account that the purpose of the rule is to ensure the Agency has the opportunity to review releases of pathogens that could entail significant exposure or risk to the environment or the public. Considerations relating to the appropriate scope of the rule will be discussed in the proposed SNUR, and the public will be invited to comment.

(2) *How to know if a microorganism is a pathogen.* Unit IV.B of this notice contains the definition of "pathogen" that the Agency will use for purposes of administering TSCA and FIFRA, and provides guidance on how to determine if a microorganism is a pathogen.

(3) *How to know if a microorganism is genetically engineered.* As discussed in Unit III.C.2.c, EPA will not require nonengineered pathogens to be reported until they are used on more than 10 acres of land (or some equivalent standard, not yet determined, for uses where acreage is an inappropriate standard). For now, a pathogen should be considered nonengineered if there has been no deliberate attempt to promote genetic changes. Any human intervention beyond removal from the environment and selection for the desired variant populations should be considered to result in an engineered microorganism.

(4) *Submitting the significant new use notice.* Persons subject to the SNUR will have to notify the Agency at least 90 days prior to any new, non-agricultural use involving environmental release of engineered pathogens. The Agency will treat nonengineered pathogens slightly differently; producers of nonengineered pathogens will be subject to significant new use notification 90 days prior to new uses involving environmental applications on more than 10 acres of land. Significant new use notifications for microorganisms should contain the same general types of information as PMN submissions for microorganisms. In all cases, SNUR notice submitters should initiate prenotice consultations with EPA well in advance of the actual submission, to expedite the Agency's review of the notice.

e. *Significant new use notice review.* EPA reviews of significant new uses of microorganisms will be conducted in a fashion similar to PMN reviews of microorganisms. The review must be completed in 90 days, extendable for good cause to 180 days. In conducting the review, EPA will use Agency and non-Agency scientists selected for their expertise on issues relevant to the specific case.

The Agency recognizes that various environmental uses of different types of pathogens pose very different levels of potential risk to human health and the environment. For example, risks should generally be lower when pathogens are applied in areas distant from host organisms; the manufacturer has used nonpathogenic strains of a pathogenic species; transferred genes are for a trait not directly involved in pathogenicity; the pathogenic source organisms have very narrow host ranges; and pathogenic genes have been deleted.

Because it recognizes these variations in risk, the Agency expects to subject some pathogenic microorganisms to more rigorous regulatory oversight than others.

3. *Research and development (R&D) exemption*—a. *Overview.* TSCA section 5(h)(3) exempts from PMN and SNUR notification requirements chemical substances manufactured in small quantities solely for R&D. However, to ensure adequate review prior to environmental release, EPA intends to require persons developing "new" microorganisms and certain engineered pathogens to notify EPA prior to any research involving environmental release. This will be accomplished by amending the PMN rule (and possibly the general SNUR rules in 40 CFR Part 721) to specify that field testing of microorganisms does not fall within the definition of "small quantities" for R&D. Until the necessary rule changes implementing this policy are final, EPA expects submitters to comply with this policy voluntarily. Notice submitters are advised to consult the Agency if they are unsure whether a particular test is subject.

b. *Background.* As explained in the December 84 notice (at page 50891), section 5(h)(3) of TSCA exempts from PMN requirements new chemical substances produced "only in small quantities solely for purposes of research and development." ("Small quantities" must be defined by rule.) The same exemption applies to substances produced for significant new uses. If this exemption as now defined were applied to living microorganisms, many microorganisms would go unreviewed by EPA until perhaps years after their initial testing in the environment. Because microorganisms can reproduce in the environment and have the potential to exhibit new traits, this has raised the question of whether these field tests for R&D purposes could present significant risks that would go unreviewed.

Because of this concern, an important issue for EPA in implementing the biotechnology program has been whether to alter the R&D exemption of TSCA section 5 notice requirements in the case of living microorganisms. EPA requested and received substantial public comments on this issue, which it considered carefully in developing this policy. The comments and EPA's response to them are described in the EPA "Response to Comments" document, available as part of the public record of this EPA notice.

c. *Rationale.* The PMN rule definition of "small quantities" for R&D has been appropriate for most chemicals subject to TSCA because of the assumption that chemical R&D generally involves limited exposure and therefore limited risk. In the case of field tests involving living microorganisms, this assumption will not always apply. Microorganisms that survive may reproduce, potentially leading to significant exposure and risks. Because of their ability to reproduce and therefore increase beyond the amount originally released, living microorganisms used in the environment cannot be considered to meet the commonly understood meaning of "small quantities" for research and development, and thus do not qualify for the exemption.

d. *Implementation.* To implement the change in the R&D exemption, EPA intends to amend the PMN rule (40 CFR 720.3(cc) and 720.36) and possibly the SNUR general provisions in 40 CFR Part 720. The amendments will specify when a microorganism is considered not to qualify for the R&D exemption, and will provide enforceable standards for that determination.

Until the R&D rule amendments are final, EPA expects commercial researchers intending to release new, living microorganisms and engineered pathogens into the environment to report their activities to the Agency as explained in the units on PMN and SNUR notification (Units III.C.1 and 2). In addition, EPA strongly encourages researchers, prior to the time of reporting, to maintain records regarding containment procedures used in their experiments. Researchers should use the definition of "environmental release" provided in Unit IV.D as a guide, ask EPA for further guidance if questions arise, and in general be as inclusive as possible in their estimation of what should be reported.

e. *Noncommercial R&D.* Noncommerical R&D is exempt from section 5 of TSCA under section 5(g) and would therefore be exempt from PMN and SNUR requirements even under the proposed amendments. EPA has defined "noncommercial" for all chemical substances subject to TSCA section 5 in a final rule published in the Federal Register of April 22, 1986 (51 FR 15096). As a general guide, R&D done by a commercial company should be considered commercial, and purely academic R&D should be considered noncommercial. For more specific guidance, the reader should examine the definition of "noncommercial" in the final rule and the discussion of "noncommercial" in the proposed PMN rule revisions published in the Federal Register of December 27, 1984 (49 CFR 50208). Readers should also note that the NIH Recombinant DNA Advisory Committee (RAC) and USDA Agriculture Biotechnology Recombinant DNA Advisory Committee (ABRAC) have jurisdiction over many noncommercial R&D activities, specifically recombinant DNA experimentation at institutions that receive funds from NIH and USDA. Both of these committees encourage submission of experiments from other sources as well.

4. *General information reporting requirements*—a. *Overview.* EPA intends to collect general information prior to the environmental use of microorganisms that are subject to TSCA, but that are not the subject of premanufacture or significant new use notification requirements. EPA will gather such information by means of a section 8(a) reporting rule. The information EPA collects will primarily be used to monitor environmental uses of microorganisms, thus making the Agency aware of cases that may require special regulatory action under other TSCA authorities. It will also be used to help the Agency evaluate and modify the scope of its biotechnology programs over time.

b. *Section 8(a) background.* Section 8(a) of TSCA authorizes EPA to issue rules requiring manufacturers, importers and processors of specified chemical substances to submit information to the Agency. TSCA section 8(a)(2) authorizes the Agency to obtain a broad range of data, including information on chemical identity and structure, production, use, exposure, disposal, and health and environmental effects. Small manufacturers, importers, and processors, as defined by EPA, are exempt from section 8(a) reporting and recordkeeping requirements, with certain statutory exceptions.

c. *Rationale for section 8(a) rule.* As explained in the overview to the EPA portion of this notice, the biotechnology review procedures described in this notice are intended to focus on the current areas of highest priority based on considerations of risk and on determinations about what makes a microorganism "new." However, there is a relatively high degree of scientific uncertainty involved in establishing these priorities at this early stage in the development of the biotechnology industry. The Agency cannot say definitively that all the microorganisms and uses that are not at this time subject to notification requirements will never need to be regulated or should never be subject to notification requirements in the future.

EPA believes that TSCA section 8(a) is the best mechanism available for determining whether specific microorganisms or categories of microorganisms not subject to PMN or SNUR notice requirements may need to be regulated. The Agency must be aware of how microorganisms are being used in the environment to fulfill its responsibility to identify and prevent important or immediate hazards that might unexpectedly arise with specific uses. The section 8(a) reporting will also provide EPA with necessary information to assess whether its overall priorities with regard to biotechnology regulation have been, in fact, appropriately set and whether they should change over time. As was pointed out by many comments on the Agency's first proposed statement on biotechnology, flexibility and incorporation of new information should be major components of any regulatory scheme.

d. *Implementation*—(1) *Who will have to report under section 8(a)?* When promulgated, EPA intends for this rule to apply to manufacturers, importers, and processors of microorganisms that are subject to TSCA and to be released in the environment, but are not otherwise reviewed under the PMN and SNUR policies described earlier. In other words, general information will be required prior to environmental releases of all microorganisms that are subject to TSCA and that are non-engineered pathogens, or that are intra-generic or naturally occurring non-pathogens.

Although the rule will apply in general to the above groups, small manufacturers, importers, and processors are usually exempt from section 8(a) reporting and recordkeeping requirements. EPA has established general exemption standards for small manufacturers (40 CFR Part 704). The Agency will consider whether these standards should be retained or altered in some way to reflect considerations particular to the biotechnology industry.

When EPA issues its notice of proposed rulemaking, the public will have an opportunity to comment on the question of who will have to report under the rule.

(2) *What information will have to be reported under section 8(a)?* EPA is in the process of considering exactly what information it will propose to require on microbial products and uses under the section 8(a) reporting rule. In deciding what information should be reported on microorganisms, EPA will consider what information is necessary for the Agency to assess the safety of planned environmental releases, to evaluate its biotechnology regulations over time, and to consider necessary and appropriate improvements. The Agency will also consider the economic impact of special information and whether the information is generally "known to or reasonably ascertainable by" potential respondents to the rule.

5. *Reporting of information on substantial risks.* All manufacturers, processors, and distributors of microbial products subject to TSCA, including those involved in research and development, are reminded of their responsibility to notify EPA immediately of any new information which "reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment" (TSCA section 8(e)).

Guidance on the section 8(e) requirement was published in the Federal Register of March 16, 1978 (43 FR 11110). Manufacturers, processors, and distributors will find that this policy statement provides general guidance on TSCA section 8(e) reporting, but it should not be considered exhaustive in terms of the types of information that would reasonably support a conclusion of substantial risk. Specifically with regard to microorganisms, the types of information that should be reported include but are not limited to (1) pathogenicity to humans, plants, animals, or microbes, (2) significant ability to displace other organisms in the intended use area, (3) significant potential to transfer genetic material to other organisms, and (4) any other significant potential to cause harm to human health or the environment.

Manufacturers, processors, and distributors should be vigilant and immediately report substantial risk information concerning microorganisms subject to TSCA.

6. *Exemptions from premanufacture notification requirements.* Section 5(h)(4) of TSCA allows EPA, by rule, to exempt from PMN requirements chemical substances that it finds will not present unreasonable risks. EPA expects to use this authority, where appropriate, to reduce the burden of PMN reporting requirements.

In its December 84 notice (at page 50891), EPA asked for comment on the issue of whether certain microorganisms or categories of microorganisms should be exempt from PMN requirements under the authority of section 5(h)(4) of TSCA. Ten respondents stated that microorganisms used in closed systems should be exempt under the 5(h)(4) provision, although several specifically remarked that appropriate biological and physical containment conditions should first be determined and met. Others suggested modifications to this approach, such as expedited reviews or reduced information requirements rather than outright exemption, or application of the exemption only to specific microorganisms or substances (e.g., *E. coli.* used in contained systems). One commenter stated that an exemption was not appropriate because there is no current Federal authority to determine safety in the event of accidental release.

Under TSCA, the PMN policy described in Unit III.C.1 extends to commercial-scale, closed system uses of microorganisms as well as environmental releases. The statute requires that all manufacturers of "new" substances must submit PMNs, regardless of whether they are used in contained facilities or open environments. Nonetheless, EPA believes that closed-system uses of new microorganisms will often present lower risks than environmental releases of the same organisms. The contained uses may therefore warrant a section 5(h)(4) exemption, and EPA is hereby announcing its intent to pursue that possibility.

Since the Agency does not yet hava sufficient information to make the necessary finding under section 5(h)(4) that such activities "will not present an unreasonable risk of injury to human health or the environment," it is soliciting more data to support that finding in the case of closed system uses. The Agency would appreciate receiving data that would support an exemption either for all inter-generic microorganisms used in closed systems, or for specific categories of such microbes. For example, a category that has been suggested for exemption is inter-generic combinations involving microorganisms that exchange DNA by known physiologic processes, and that are on the NIH RAC exchanger list. This possible exclusion is mentioned in the OSTP preamble published in this **Federal Register.**

Information and data relevant to this issue should be sent to EPA at the address listed at the beginning of this notice.

In addition to supporting the use of section 5(h)(4) exemptions, the Agency will try to identify categories of microorganisms that pose lower risk even though they may not meet the necessary findings for exemption. In such cases, the Agency will consider reducing the burden of PMN reporting by lowering the information requirements associated with the PMN, and by conducting expedited reviews. The Agency requests any data or information that could be used to support exemptions or expedited reviews.

IV. Definitions of Terms for Regulatory Purposes

As explained in the previous units of this notice, EPA intends at this time to focus its regulatory programs on microorganisms containing genetic material from dissimilar source organisms (defined as organisms from different genera), pathogenic microorganisms, microorganisms containing genetic material from pathogens, nonindigenous microorganisms, and TSCA nonagricultural environmental applications. Applicable requirements are described in Units II and III of this notice. The purpose of this unit is to provide detailed information on how a person should determine whether a specific product is a pathogen, contains genetic material from a pathogen, contains genetic material from organisms of different genera (inter-generic combination), is nonindigenous, is released to the environment, or is used for nonagricultural TSCA purposes.

A. How To Determine if a Product Is an Inter-Generic Combination

For purposes of implementing its concept of "new" microorganisms, the Agency is defining "new" microorganisms as those formed by deliberate combinations of genetic material from organisms of different genera.

This standard is purposely based on the taxonomic designations of microorganisms. While imperfect in many ways, taxonomy appears to provide the best available standard for "dissimilarity" among organisms, for the following reasons:

1. Although subject to periodic revision within the scientific community, taxonomy is a common language used by scientists to describe how organisms are similar and dissimilar (Refs. 4, 18).

2. Taxonomy reflects the most recent scientific observations about phenotypic and genotypic differences between organisms.

3. Taxonomy provides a universally available point of reference that can be understood by industry and enforced by the Agency.

4. EPA expects microorganisms being used in biotechnology research and development will have or can be assigned clear taxonomic designations; therefore, the use of taxonomic standards imposes few if and additional requirements on industry.

5. There is a significant adminstrative advantage to independently established criteria such as taxonomic standards, because EPA will not have to create and maintain a separate set of criteria for regulatory purposes.

The Agency expects all manufacturers to know or determine the currently accepted designations (genus, species) of the source organisms they have used in producing microbial products subject to FIFRA and TSCA. In addition, EPA expects submitters to use taxonomic literature and taxonomic experts, if necessary, to determine the correct identity of their microorganisms. A number of commenters on the December 84 notice stated that organisms manipulated by modern genetic engineering will in most cases already be well characterized. This fact should make implementation of this policy relatively easy in most cases.

Excluded from this policy on inter-generic combinations are microorganisms that have resulted from the addition of inter-generic material that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators, and ribosome-binding regions.

"Well-characterized, non-coding regulatory regions" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

EPA emphasizes that this policy excludes only inter-generic combinations that have resulted solely from the addition of well-characterized, non-coding regulatory regions. If the final microorganism contains any regions from organisms of other genera that do not meet this restriction, such as coding regulatory regions or any poorly characterized regions, the microorganisms is considered new and does not come under the exclusion for regulatory regions discussed above.

To document these features, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies relied upon, or data from tests performed to determine the above characteristics.

If persons do not know the genera of particular organisms, they should consult standard sources such as the following:

i. Bacteria

(1) Skerman, V.B.D., V. McGowan, and P.H.A. Sneath. 1980. Approved list of bacterial names. International Journal of Systematic Bacteriology 30:225–420.

(2) Moore, W.E.C., E.P. Cato, and L.V.H. Moore. 1985. Index of the bacterial and yeast nomenclature changes published in the International Journal of Systematic Bacteriology since the 1980 approved list of bacterial names (1 January 1980 to 1 January 1985). International Journal of Systematic Bacteriology 35:382–407.

Manufacturers should consult issues of the International Journal of Systematic Bacteriology for validly published names and for names placed on Validation Lists since January 1985.

ii. Algae

(1) DeToni, 1889. Sylloge Algarum.

(2) Index Kewensis. 1895-present. (Royal Botanical Gardens, Kew.)

iii. Protozoa

(1) Nomenclator Zoologicus. 1758-present. Published in four volumes and two supplements from 1939 onwards. Edited by S.A. Neave. Zoological Society, London.

(2) Index Zoologicus. 1800–1900. Charles Owen Waterhouse. (Published 1902.) Edited by David Sharpe. Zoological Society, London.

(3) Index Zoologicus. 1902-present. (Zoological Society, London.)

iv. Fungi

(1) Saccardo, P.A. 1882–1921. Sylloge Fungorum. (Pavia, 25 vol.)

(2) Clements, F.E. and C.L. Shear. 1931. The Genera of Fungi (H.W. Wilson and Co., N.Y.)

(3) Index to Fungi. 1940-present. Commonwealth Mycological Institute, Kew, Surrey, England.

(4) Petrak's List of Fungal Names. 1922–1940. Commonwealth Mycological Institute, Kew, Surrey, England.

(5) Hawksworth, D.L., B.C. Sutton, and G.C. Ainsworth. 1983. Ainsworth and Bisby's Dictionary of the Fungi. Commonwealth Mycological Institute, Kew, Surrey, England.

v. Viruses

(1) Mathews, R.E.F. 1979. Classification and nomenclature of viruses, 3rd report of the International Committee on Taxonomy of Viruses. Intervirology 12(3–5):1–199.

If the taxonomic positions of source organisms are ambiguous or if the boundaries of a genus are in dispute, the Agency expects the submitter to be aware of these controversies. Ambiguities at the species level or lower will not affect the FIFRA and TSCA policies. However, if the taxonomy at the genus level is controversial, such that organisms may be considered by some to belong to the same genus and by others to belong to different genera, the submitter must comply with the applicable requirements of FIFRA or TSCA, or come to EPA for a case-specific determination (address provided at the beginning of this notice). In general, submitters should expect that microorganisms will be considered inter-generic if the taxonomy of either source organism, at the genus level, is controversial.

In the case of chemically synthesized genes, the Agency will follow a similar principle. The genetic sequence of the synthesized gene may be identical to a sequence known to occur in an organism in the same genus as the recipient microorganism. If so, the resulting microorganism will be considered intra-generic. However, the producer should be prepared to document how it made this determination. Conversely, the sequence of the synthesized gene may be different or not known to be identical to a sequence in the genus of the recipient microorganism. In this case, the resulting product will be considered inter-generic.

EPA's definition of inter-generic combinations contains a standard of intent on the part of the manufacturer or producer. Inter-generic combinations that occur as unintentional byproducts of microorganisms coming in contact with one another will not be considered subject to the provisions of TSCA and FIFRA that apply to inter-generic combinations. For example, inter-generic combinations may occur at very low frequencies if microorganisms from different genera are applied to the same plot of land, or are sold together as mixtures. Similarly, if manufacturers develop microorganisms that are naturally infected with viruses, and if the developer did not intend to promote and did not provide conditions actively promoting the infection of the microorganisms with the naturally occurring viruses, then the microorganisms containing naturally occurring inter-generic combinations would not be considerd inter-generic under the FIFRA and TSCA policies.

On the other hand, if the manufacturer or producer intentionally provides conditions to promote genetic transfer, or if inter-generic microorganisms are primary components of a product or mixture, then the microorganisms will be considered inter-generic and subject to the applicable provisions of FIFRA and TSCA.

Submitters should consult the Agency if they have any questions about these distinctions.

B. How to Determine if a Product Is a Pathogen

For the purposes of this policy, a pathogen is defined as a virus or organism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, or microorganisms). A disease is an abnormal physiological function in an organism, occurring as a consequence of the activity of proliferating microorganisms directly associated with or infecting the host organism, or due to biologically active substances such as toxins, antibiotics, or growth regulators produced by a microorganism (Refs. 5, 6, 7, 8, 14, 19).

This policy is not meant to include such organisms as competitors or colonizers of the same substrates, commensalistic or mutualistic microorganisms, or opportunistic pathogens. However, if a microorganism has more than one mechanism for affecting other organisms and one of these is pathogenicity, then the microorganism is considered to be a pathogen.

A microorganism will be subject to EPA policies regarding pathogens if:

1. The organism belongs to a pathogenic species or to a species containing pathogenic strains, according to sources identified by EPA below, or from information known to the producer that suggests that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic according to sources identified by EPA, or information known to the producer and EPA; an example of a nonpathogenic strain of a pathogenic species is *Escherichia coli* K–12; examples of nonpathogenic species are *Bacillus subtilis, Lactobacillus acidophilus,* and *Saccharomyces* species; or,

2. The organism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item 1, above. An exception to this requirement is a genetically engineered organism developed by transferring well-characterized, non-coding regulatory regions from a pathogenic donor to a nonpathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

To document these items, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies, or data from tests performed to determine the above characteristics.

The Agency is excluding genetically engineered organisms containing material from pathogens if the material transferred is from a pathogenic donor to a nonpathogenic recipient, and consists solely of well-characterized, non-coding regulatory regions. In this case, the transferred material does not code for traits directly associated with pathogenicity. The Agency believes that these organisms do not pose significant risks because they do not possess new combinations of traits or pathogenic traits, but instead exhibit quantitative changes in preexisting traits in a nonpathogenic recipient.

The Agency is excluding opportunistic pathogens for two reasons. First, in terms of risk priorities, outright pathogens are of significantly greater concern than organisms that would not act as pathogens except under unusual circumstances. Second, because of the very large number of microorganisms that could be considered to be opportunistic, their inclusion would result in an inappropriately restrictive policy.

There are a number of standard sources that can be used to determine whether a microorganism belongs to a pathogenic species. EPA is compiling a list of such sources, and is considering developing a list of pathogenic species, as part of future rulemaking activities. As interim guidance, persons should consider sources such as the following:

(1) Anne, W., ed. 1980. Fish Diseases. Springer-Verlag, New York.

(2) Anver, M.R. and C. Pond. 1984. Biology and Diseases of Amphibians. In Laboratory Animal Medicine, J.G. Fox, B.J. Cohen, F.M. Loew, eds. Academic Press, Orlando, FL.

(3) Bliss, D.E., ed. 1982–1985. Biology of Crustaceans (Volume 6 Pathobiology). Academic Press, New York.

(4) Blood, D.C., J.A. Henderson, and O.M. Radostits. 1979. Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pigs, and Horses. 5th edition. Lea & Febiger, Philadelphia, PA.

(5) Braude, A. 1988. Medical Microbiology and Infectious Diseases. 2nd edition. W.B. Saunders, Philadelphia, PA.

(6) Buchanan, A.M. 1982. Veterinary Microbiology. Elsevier Scientific, Amsterdam.

(7) Buchanan, R.E. and N.E. Gibbons, eds. 1974. Bergey's Manual of Determinative Bacteriology. 8th edition. Williams and Wilkins Co., Baltimore.

(8) Cantwell, G.E., ed. Insect Diseases, M. Dekker, New York.

(9) Commonwealth Mycological Institute. Descriptions of Plant Pathogenic Bacteria, Fungi, and Viruses. Commonwealth Agricultural Bureaux, Kew, Surrey, England.

(10) Davidson, E., ed. 1981. Pathogenesis of Invertebrate Microbial Diseases. Allanheld, Osmum, Totowa, NJ.

(11) Ellis, A.E., ed. 1985. Fish and Shellfish Pathology. Academic Press, London.

(12) Gherna, R., W. Nierman, and P. Pienta, eds. 1985. Catalogue of Bacteria, Phages, rDNA Vectors. 16th edition. American Type Culture Collection, Rockville, Maryland.

(13) Hagan, W.A. and D.W. Bruner. 1981. Hagan and Bruner's Infectious Diseases of Domestic Animals: With Reference to Etiology, Pathogenicity, Immunity Epidemiology, Diagnosis and Bilogic Therapy. 7th edition. Comstock Publishing Associates, New York.

(14) Hitchner, S.B., ed. 1980. Isolation and Identification of Avian Pathogens. 2nd edition. American Association of Avian Pathologists, College Station TX.

(15) Jacobson, E. 1984. Biology and Diseases of Reptiles. In Laboratory Animal Medicine, J.G. Fox, B.J. Cohen, F.M. Loew, eds, Academic Press, Orlando, Fl.

(16) Jong, S.C. and M.J. Gantt, eds. 1985. Catalogue of Fungi/Yeasts. 16th edition. American Type Culture Collection, Rockville, Maryland.

(17) Kinne, O. 1980–1983. Diseases of Marine Animals. Vol. I. General Aspects, Protozoa to Gastropoda, published by John Wiley, Vol. II Bivalvia to Arthropoda, Vol. III, Echinodermata to Vertebrata, Vol. IV, Pisces Applied Aspects, Volumes II–IV published by Biologische Anstalt, Helgoland, Germany.

(18) Krieg, N.R. and J.G. Holt, eds. 1984. Bergey's Manual of Systematic Bacteriology, Vol. I, Williams and Wilkins Co., Baltimore, MD.

(19) Marcus, L.C. 1981. Veterinary Biology and Medicine of Capitve Amphibians and Reptiles. Lea and Febiger, Philadelphia, PA.

(20) Padhye, A.A. 1978. Fungi pathogenic to Man and Animals. In A.I. Laskin and H.A. Lechevalier, eds. Chemical Rubber Company. Handbook of Microbiology, 2nd edition, Volume II, pp. 319–340.

(21) Sparks, A.K. 1985. Synopsis of Invertebrate Pathology Exclusive of Insects. Elsevier, Holland.

(22) Starr, M.P., H. Stolp, H.G. Truper, A. Balows, and H.G. Schlegel, eds. 1981. The Prokaryotes—A Handbook on Habitats, Isolation, and Identification of Bacteria. Vols. 1 and 2. Springer-Verlag.

(23) Steinhaus, E.A., ed. 1963. Insect Pathology: An Advanced Treatise. Academic Press, New York.

(24) U.S. Department of Agriculture. 1960. Index of Plant Diseases in the United States. Crops Research Division, Agriculture Research Service. Agriculture Handbook No. 165.

(25) U.S. Department of Health, Education, and Welfare. 1977. Classification of Etiologic Agents on the Basis of Hazard. In A.I. Laskin and H.A. Lechevalier, eds. Chemical Rubber Company Handbook of Microbiology, 2nd edition, Volume I, pp. 559–573.

(26) U.S. Department of Health and Human Services. 1984. Biosafety in Microbiological and Biomedical Laboratories. Public Health Service, Centers for Disease Control, Atlanta, GA.

(27) Whiteman, C.E., and A.A. Bickford. 1983. Avian Diseases Manual. 2nd edition. American Association of Avian Pathologists. Kennett Square, PA.

The Agency expects that producers will be sufficiently familiar with the relevant literature and the species of the microorganisms under development that the pathogenicity or lack of it will already be known. Therefore, the Agency does not believe that determining whether a microorganism belongs to a pathogenic species based on published sources will be burdensome.

Where there is disagreement among sources about whether a strain belongs to a pathogenic species, the submitter must assume that it belongs to a pathogenic species, or come to EPA for a case-specific determination (address provided at the beginning of this notice).

As part of further rulemaking, the Agency plans to develop a list of nonpathogenic strains of pathogenic species, in addition to *E. coli* K–12, that will be exempt from Agency policies for pathogenic microorganisms. In the interim, if a submitter is using a strain that belongs to a pathogenic species, except *E. coli* K–12, the submitter should assume that it is pathogenic.

Because of the pathogenic potential of most, if not all, viruses, and because the species concept does not generally apply in virus taxonomy, the Agency will consider any product that is or contains genetic material from a virus to be a pathogen.

The Agency intends to update this guidance periodically, particularly the list of publications.

C. How To Determine if a Product Is a Nonindigenous Microorganism

A microorganism will be considered nonindigenous to any one of the geographic areas listed below if it is isolated from outside that area:

1. The continental United States, including Alaska, and the immediately adjoining countries (i.e., Canada and Mexico).
2. The Hawaiian Islands.
3. The Caribbean Islands including Puerto Rico and the U.S. Virgin Islands.

For example, a microorganism from Hawaii, developed for use as a microbial pesticide in the continental U.S., will be considered to be nonindigenous to the continental United States. Under FIFRA, the Agency would therefore be notified before initiation of small-scale field testing of the microbial pesticide in the continental U.S.

In normal usage, nonindigenous organisms are generally considered to be naturally occurring organisms placed in environments where they are not native or have not evolved. This concept means that a microorganism could be considered nonindigenous to an ecosystem that is adjacent to the one in which it evolved, nonindigenous to ecosystems far removed, or even indigenous to nearby or far-removed ecosystems. This happens for a number of reasons such as the widely varying effects of geographic barriers as isolating mechanisms; microbial dispersal mechanisms; and the biological, chemical, and physical features shaping different environments. Given the complexity and impracticality of determining whether a particular microorganism is indigenous to a wide range of habitats that may exist within regions and states, the Agency has selected continental boundaries to describe geographic regions that are clearly isolated and are easily used for administrative purposes. These boundaries will be used to determine whether a microorganism is nonindigenous and hence subject to particular provisions under FIFRA (see Unit II).

D. How To Determine if a Product Is Released to the Environment

In the future, it is likely that a definition of environmental release will be developed. In the interim, the Agency's approach will focus on when a microorganism is considered to be contained rather than when it is released.

A microorganism will be considered environmentally contained if the microorganism is used in a laboratory that complies with NIH RAC guidelines; or the microorganism is used in a contained greenhouse, fermenter, or other contained structure. In general, "contained greenhouse, fermenter, or other contained structure" means a building or structure that has a roof and walls. It should also have a ventilation system to minimize microbial release to the outdoors, a system for sterilizing water runoff and wastes, and a system for restricting insects, if any of these are plausible routes for dissemination of microorganisms. Experimenters should control pests, sterilize soil or other material containing microorganisms before disposal or reuse, and generally limit access only to those persons who must have access for research purposes.

E. How to Determine if a Product Is Used for Nonagricultural Purposes

An agricultural use of a microorganism is any use or application, the primary purpose of which is to produce, enhance, or cultivate plants or animals. The definition is not meant to include pesticides.

F. Definition of Plants and Animals

For the purposes of this EPA notice, plants are defined as multicellular organisms characterized by eukaryotic cell walls, photosynthetic ability, and embryonic development. Members include mosses, liverworts, and vascular plants (including most terrestrial crop plants). Animals are defined as multicellular organisms composed of eukaryotic cells with ingestive nutrition and lacking rigid cell walls and photosynthetic ability. Members include coelenterates, flatworms, molluscs, segmented worms, arthropods, echinoderms, and vertebrates.

V. References

The following books, articles, and reports were used in preparing this notice:

(1) Agrios, G.N. 1978. Plant patbology. Academic Press, New York, NY.
(2) Campbell, A. 1978. Tests for gene flow between eucaryotes and procaryotes. Journal of Infectious Diseases 137: 681–685.
(3) Covello, V.T. and Fiksel, J.R., eds. 1985. The suitability and applicability of risk assessment methods for environmental applications of biotechnology. National Science Foundation, Report #NSF/PRA 8502286, Washington, DC.
(4) Curtis, H. 1983. Biology. Worth Publishers, Inc., New York, NY.
(5) Cruickshank, R., J.P. Duguid, B.P. Marmion, and R.H.A. Swain. 1973. Medical microbiology, Vol. 1: Microbial infections. Churchill Livingstone, Edinburgh.
(6) Davis, B.D., R. Dulbecco, H.N. Eisen, H.S. Ginsberg, W.B. Wood, Jr., M. McCarty. 1980. Microbiology, Harper and Row, New York, NY.
(7) Freeman, B.A. 1979. Burrows textbook of microbiology. W.B. Saunders Co., Philadelphia, PA.
(8) Fuerst, R. 1983. Microbiology in health and disease. W.B. Saunders Co., Philadelphia, PA.
(9) Gillett, J., Levin, S., and Stern, A. 1985. Potential impacts of environmental release of biotechnology products: Assessment, regulation, and research needs. Cornell Ecosystems Research Center, ERC–075, Ithaca, NY.
(10) Lewin, B. 1983. Genes. John Wiley and Sons, New York, NY.
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VI. Public Record

EPA has established a public record for this statement of policy (docket number OPTS–00049A) which is available to the public in the OTS Public Information Office, 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

The Public Information Office is located in Rm E–107, 401 M St. S.W.,

Washington, D.C. 20460. The record includes all information considered by EPA in formulating this policy. The record includes the following categories of information:

1. Federal Register notices.
2. Support documents and reports.
3. Public comments, summaries of comments, and EPA's responses to comments on the EPA December 1984 Notice on biotechnology (49 FR 50860).
4. Communications.

The record also includes, by reference, published literature cited in this policy statement and generally available.

The docket of the record detailing its specific contents is available in the OTS Reading Room.

VII. Regulatory Assessment Requirements

A. Regulatory Flexibility Act

As required by the Regulatory Flexibility Act (5 U.S.C. 605(b)), EPA has assessed the impact of the immediately effective aspects of this policy on small businesses. EPA has determined that the immediately effective requirements will not create additional impacts on small businesses over those already identified in the final PMN rule, 40 CFR Part 720, and the Interim Policy for small-scale field testing of microbial pesticides (49 FR 40659).

B. Paperwork Reduction Act

The information collection requirements contained in this policy have been approved by the Office of Management and Budget (OMB) under provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 et seq. and have been assigned OMB control numbers 2070–0012 and 2070–0069.

DEPARTMENT OF AGRICULTURE

Final Policy Statement for Research and Regulation of Biotechnology Processes and Products

AGENCY: Department of Agriculture.

ACTION: Final policy statement.

SUMMARY: This statement presents, in final form, an explanation of the U.S. Department of Agriculture (USDA) policy for research and regulation of biotechnology applications in agrilculture and forestry. New Information is provided about policy for agricultural biotechnology research, proposed regulations, and scientific review mechanisms. The document also contains responses to comments and clarifications of the USDA policy statement published in the **Federal Register** on December 31, 1984 (49 FR 50897–50904).

FOR FURTHER INFORMATION CONTACT: For regulatory activities, contact Dr. James W. Glosser, Associate Administrator, Animal and Plant Health Inspection Service (APHIS), USDA, Room 313–E Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250, telephone Area Code (202) 447–3580. For research activities, contact Dr. John Patrick Jordan, Administrator, Cooperative State Research Service (CSRS) USDA, Room 304–A, Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250, telephone Area Code (202) 447–4423.

All written documents received by USDA on this notice are available for public inspection in Room 313–E Administration Building, 12th and Independence Avenue, SW., Washington, DC, weekdays between 8:00 a.m. and 4:00 p.m.

Table of Contents

I. Introduction

The USDA portion of the "Proposal for a Coordinated Framework for Regulation of Biotechnology" (hereafter referred to as the December 31, 1984 Notice) appeared at 49 FR 50897–50904. As a part of its policy perspective, USDA stated that agriculture and forestry products developed by biotechnology will not differ fundamentally from conventional products and that the existing regulatory framework is adequate to regulate biotechnology.

USDA has both research and regulatory responsibilities for biotechnology activities. This document provides significant new information in both areas. Section II describes 1985 **Federal Register** notices concerning USDA policies and responsibilities for biotechnology. Included in this discussion is an explanation of the assignment of responsibilities within USDA for the oversight of USDA funded research and for the regulation of the products of biotechnology. An understanding of the way in which USDA has divided these responsibilities should prove helpful to those in the private sector seeking review and/or approval of biotechnology applications.

A new section III has been added describing USDA's policy for agricultural biotechnology research. USDA is publishing as a companion document, USDA Guidelines for Biotechnology Research that will closely parallel the NIH Guidelines. The USDA guidelines will be issued under the authority of the Food Security Act of 1985 (Pub. L. 99–198). This Act amended section 1404(2) of the National Agriculture Research, Extension, and Teaching Policy Act (NARETPA). The Amendment gave the Secretary of Agriculture responsibility for establishing "appropriate controls with respect to the development and use of the application of biotechnology to agriculture." All USDA funded agriculture biotechnology research or research conducted at an entity receiving USDA funds would be subject to the USDA Guidelines for Biotechnology Research unless the specific research project is supported by and subject to the guidelines or regulations of another Federal agency. These Guidelines would encompass all phases of agricultural biotechnology research, i.e. (1) Contained laboratory experiments; (2) specialized isolation research (e.g., greenhouse, biotron); and (3) environmental research release (e.g., controlled and segregated field plots). USDA hopes that entities not required to comply with the Guidelines would voluntarily adhere to the requirements. To encourage compliance, USDA proposes to adopt the NIH policy of providing the researchers not required to comply with these Guidelines the opportunity to have their new biotechnology research proposals reviewed by USDA.

Those entities covered by the USDA Guidelines for Biotechnology Research would also be required to comply with any applicable statutes such as those set forth in section IV of this document, and any regulatory issues thereunder.

The Secretary of Agriculture has established an Office of Agriculture Biotechnology (OAB), which will have primary responsibility for implementing and coordinating the Department's policies and procedures pertaining to all facets of biotechnology. This includes the conduct of laboratory and field research, exprimentation on biotechnology products prior to their commercialization, and all matters of oversight of biotechnology in agriculture. The new office will report to the Assistant Secretary for Science and Education through the authority provided in the amendment to the Food Security Act of 1985. The Assistant Secretary for Science and Education will seek to establish an Agriculture Biotechnology Recombinant DNA

Advisory Committee (ABRAC) and shall continue the responsibilities for agriculture formerly handled by the NIH–RAC during the last 10 years. The OAB shall operate in a close parallel manner to the Office of Recombinant DNA Activities (ORDA) of the National Institutes of Health. This includes the responsibility of the ABRAC and the implementation of the USDA Guidelines for Biotechnology Research. The NIH system is well respected both domestically and worldwide, and has achieved a high degree of efficiency in achieving broad confidence in the safety of new biological research conducted under its requirements.

The OAB also will serve as a focal point for coordinating a National Biological Impact Assessment Program, which is to evaluate and monitor the potential impacts of biotechnological processes and products on safety and the environment.

Section IV contains USDA's regulatory policy statements for veterinary biological products, plants and plant products, meat and poultry products, and seeds. USDA stated in the December 31, 1984 Notice that while its existing regulatory framework is adequate, it would constantly reevaluate its regulatory position and should additional regulatory measures become necessary, amend its regulations (49 FR 50904). For veterinary biologicals regulated under the Virus-Serum-Toxin Act (VSTA), USDA has identified three categories which may be derived by recombinant DNA techniques or developed from hybridomas. The categories are based on biological characteristics and safety concerns, and are described fully in section IV(A). The first category consists of inactivated recombinant DNA-derived vaccines, bacterins, bacterin-toxoids, virus subunits, or bacterial subunits, as well as monoclonal products. This category presents no new or unusual safety or environmental concerns. The second category includes those products containing live microorganisms that have been modified by the addition or deletion of one or more genes. Such products will be evaluated under current regulatory policies and procedures to assure that the addition or deletion of specific genetic information does not impart increased virulence, pathogenicity, or survival advantages. The third category includes products using live vectors to carry recombinant derived foreign genes for immunizing antigens and/or other immune stimulants. Characteristics of safety and transmission must be established fully before questions and concerns dealing with safety to humans, animals, and release into the environment can be answered and before such products can be considered for licensing. Section IV(A) also includes new information about revised USDA review procedures for the importation of cell cultures and hybridomas. A brief discussion is included about the proposed regulations implementing the provisions of the amendments to the VSTA contained in the Food Security Act of 1985.

For organisms and products derived by the techniques of genetic engineering, USDA is proposing new rules to regulate organisms which are plant pests or which there is reason to believe are plant pests. It is USDA's policy to regulate certain genetically engineered organisms if the donor, vector/vector agent, or recipient organism is a member of a group of organisms that are known to contain plant pests, or if based on experience, USDA determines that a genetically engineered organism or product is a plant pest or if USDA has reason to believe that a genetically engineered organism or product is a plant pest. The proposed regulations are summarized in section IV(B).

The USDA policy for regulating meat and poultry products and seeds derived through biotechnology remains substantially as stated in the December 31, 1984 Notice, and appears in section IV (C) and (D).

A new section (V) has been added describing the scientific review mechanisms to be established by USDA to assist USDA Agencies in biotechnology research and regulatory decision-making. USDA has established a Committee on Biotechnology in Agriculture (CBA) chaired by the Assistant Secretary for Science and Education and the Assistant Secretary for Marketing and Inspection Services.

A detailed summary of comments on the December 31, 1984 Notice and USDA responses appears as section VI. The comments are organized to conform to the form of the December 31, 1984 Notice, with general comments and responses on the USDA regulatory philosophy followed by comments and responses on specific aspects of USDA's regulatory structure.

II. Notices

Three **Federal Register** notices concerning the Department's biotechnology related activities have been published subsequent to publication of the December 31, 1984 Notice.

On July 19, 1985, a document amending the delegations of authority of USDA to assign responsibility for these research and regulatory activities (7 CFR Part 2) was published in the **Federal Register** (50 FR 29367–29368).

In this document, the Secretary of Agriculture delegated responsibility to the Assistant Secretary for Marketing and Inspection Services to coordinate the development and carrying out of all matters and functions pertaining to the Department's regulation of biotechnology and to act as liaison on all matters and functions pertaining to the regulation of biotechnology between agencies within the Department and between the Department and governmental and private organizations. These responsibilities were further delegated from the Assistant Secretary for Marketing and Inspection Services to the Administrator of the Animal and Plant Health Inspection Service (APHIS).

Also in this document, the Secretary of Agriculture delegated responsibility to the Assistant Secretary for Science and Education to coordinate the development and carrying out of all matters and functions pertaining to agricultural research involving biotechnology conducted or funded by the Department including the development and implementation of guidelines for oversight of research activities, and to act as liaison on all matters and functions pertaining to agricultural research in biotechnology between agencies within the Department and between the Department and other governmental, educational and private organizations.[1]

On September 23, 1985, USDA's APHIS published a notice which contained its policy statement and requirements for the control and protection of documents that contain confidential business information concerning biotechnology and the veterinary biologics program (50 FR 38561–38563).

On November 14, 1985, the Office of Science and Technology Policy published a notice in the **Federal Register** announcing the establishment of the Biotechnology Science

[1] The Assistant Secretary for Science and Education oversees the research activities of the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), the Extension Service (ES), and the Office of Grants and Program Systems (OGPS). The Assistant Secretary for Marketing and Inspection Services oversees the regulatory activities of the Animal and Plant Health Inspection Service (APHIS), which includes Veterinary Services (VS) and Plant Protection and Quarantine (PPQ); the Agricultural Marketing Service (AMS); and the Food Safety and Inspection Service (FSIS). The policies and procedures of these agencies for biotechnology were described in the USDA portion of the coordinated policy statement at 49 FR 50899–50904

Coordinating Committee (BSCC) (50 FR 47174–47195). This Committee is to serve as an interagency forum for coordinating science issues related to research and commercial applications of biotechnology. The notice also stated that USDA will establish a Committee on Biotechnology in Agriculture (CBA) to assist in assuring that research and regulatory decisions are based on the best science available.

III. USDA Research Policy Statement

USDA supports research to promote and protect the general health and welfare of the people of the United States.[2] Research program include: Studies on production of food and agricultural processing and marketing; identity and development of new crop and animal sources of food, fiber, and energy; increased agricultural efficiency and reduction of dependence on petroleum-based products; development of improved management and conservation of soil, water, forest, and range resources. The programs are fulfilled through State, Federal, and private industry cooperative efforts.

In the areas of agricultural research relevant to biotechnology, many plant, animal, and microbial alterations have been developed for release through traditional genetic approaches such as mutagenesis and hybridization. In a complementary vein, beneficial introduction of organisms from abroad have established a sound base for research and regulatory oversight. The experience with these bases provide a substantial knowledge base for conducting evaluations of the safety and efficacy of biotechnology processes and products.

USDA will evaluate the environmental impacts in the context of individual experiments that encompass the entire range of experimentation from contained facilities to open field testing. As knowledge and experience are gained, broadly applicable procedures and guidelines will be developed. Particular consideration will be given to the stability of engineered changes and the possibility that genetic elements might be transferred from one organism to another. Also important will be the development of data that will enable predictions of which organisms may become established in new ecosystems, and resulting environmental consequences.

USDA considers products developed through biotechnological techniques as no different from those products resulting from research using conventional techniques providing appropriate research review is conducted with established protocols. Agricultural biotechnology research activities require appropriate review to avoid untoward effects on human health and the environment.

USDA expects to rely on the existing network of scientific expertise in the agriculture research community. Thousands of plant selections, animal breeding lines, and microorganisms are tested annually at sites under varying climatic conditions through the Nation. This network of scientific expertise permits continual, open assessment of agricultural research and products of that research in the field. USDA has broad statutory authority to conduct and support research in wide ranging areas of agriculture. In addition to the authorities described in the matrix of Federal Laws related to biotechnology found in the **Federal Register** Notice of November 14, 1985 (50 FR 47174–47195) the Food Security Act of 1985 (Section 1404(2) of the National Agriculture Research, Extension, and Teaching Policy Act Amendments of 1985, Pub. L. No. 99–198), made the Secretary of Agriculture responsible for establishing "appropriate controls with respect to the development and use of the application of biotechnology to agriculture." Through this authority, and pursuant to the Delegation of Authority Pertaining to Biotechnology published in the **Federal Register** on July 19, 1985 (50 FR 29367–68), the Assistant Secretary for Science and Education will complete development of a national system of agricultural biotechnology research oversight in much the same manner that agriculture has been a part for the last 10 years through the NIH–RAC.

The Assistant Secretary for Science and Education has initiated the establishment of the Agriculture Biotechnology and Recombinant DNA Advisory Committee (ABRAC), to be managed through an Office of Agriculture Biotechnology (OAB) which is a parallel to the National Institutes of Health Recombinant DNA Advisory Committee (NIT–RAC) and Office of Recombinant DNA Activities (ORDA). The OAB will serve as the focal point for developing and coordinating USDA policies and activities pertaining to biotechnology research and will perform related interagency and public liaison functions. OAB will also assist in carrying out the responsibilities assigned to the Assistant Secretary for Science and Education, including the development and implementation of policies and procedures, and guidelines for the conduct of laboratory and field research.

All federally-funded agriculture biotechnology research or reseach conducted at an entity receiving USDA funds will be subject to the USDA Guidelines for Biotechnology Research, which are published as a companion document to this policy statement, unless the specific research project is supported by and subject to the guidelines or regulations of another Federal agency. These Guidelines encompass the entire spectrum of degrees of containment in agricultural biotechnology research i.e.: (1) Contained laboratory experiments; (2) specialized isolation research (e.g., greenhouse, biotron); and (3) environmental research agricultural biotechnology release (e.g., controlled and segregated field plots). Research investigators not required to comply with USDA Guidelines will be encouraged to follow these Guidelines. To assure consistency, USDA adopted the model established by the NIH of providing such researchers with the opportunity to have their biotechnology research proposals reviewed as required by the Guidelines.

The USDA Guidelines for Biotechnology Research require that research organization use the Institutional Biosafety Committee (IBC) concept as established by NIH. This requirement assures that each research organization and its investigators employ a multidisciplinary team to assist in carrying out their responsibilities under the Guidelines. The IBC's, as described in the Guidelines, would consist of persons with relevant agricultural expertise in areas such as recombinant DNA technology, biological safety, physical containment, and ecology. Requests for review beyond IBC should be sent to the Office of Agriculture Biotechnology (OAB) through the Assistant Secretary of Science and Education, Room 324–A, Administration Bldg., Washington, D.C. 20250.

These Guidelines also would require compliance with existing statutes of the USDA involving the movement of regulated organisms that require the issuance of a permit. The movement of microorganism injurious to plants and animals as well as the movement of certain non-indigenous plants and animals would continue to follow long-established procedures for USDA approval. After review, a permit, if needed, may be issued that allows movement. It is the responsibility of the research scientists to obtain that permit.

[2] See Addendum for Research Legislative Authorities.

The Assistant Secretary for Science and Education will complete establishment of a National Biological Impact Assessment Program (NBIAP) as indicated in the USDA Guidelines for Biotechnology Research. NBIAP would serve to assist USDA in the evaluation and monitoring of biotechnology research and impact over time. Coordination of NBIAP will be provided through OAB.

IV. USDA Regulatory Policy Statements

The existing USDA regulatory authority for biotechnology was listed in the matrix of the December 31, 1984 Notice at 49 FR 50860–50874 and described in brief at 49 FR 50898–50899. The statutes considered most applicable to biotechnology applications are the Virus-Serum-Toxin Act (VSTA) of 1913 (21 U.S.C. 151–158), the Federal Plant Pest Act (FPPA) of May 23, 1957 (7 U.S.C. 150aa–150jj), the Plant Quarantine Act (PQA) of August 20, 1912 (7 U.S.C. 151–164, 168, 167), the Organic Act of September 21, 1944 (7 U.S.C. 147a), the Federal Noxious Weed Act (FNWA) of 1974 (7 U.S.C. 2801 *et seq.*), the Federal Seed Act (FSA) (7 U.S.C. 551 *et seq.*), the Plant Variety Protection Act (PVPA) (7 U.S.C. 2321 *et seq.*), the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 *et seq.*), and the Poultry Products Inspection Act (PPIA) (21 U.S.C. 451 *et seq.*).

A. Veterinary Biological Products

Under the Virus-Serum-Toxin Act of 1913, 21 U.S.C. 151–158, the USDA exercises regulatory authority over all veterinary biologics imported into the United States or shipped or delivered for shipment interstate. Recent amendments contained in the Food Security Act of 1985 have extended this authority to products which are shipped intrastate or exported, and have given the Department additional enforcement mechanisms such as the power to detain and seize products. Under the VSTA, veterinary biologics may not be shipped or delivered for shipment if they are worthless, contaminated, dangerous, or harmful. Veterinary biological products must be prepared in a USDA-licensed establishment under regulations promulgated by the Secretary of Agriculture. Those products which are imported into the United States must be imported under a permit issued by the Secretary. The pertinent regulations for veterinary biologics are found in Title 9 of the Code of Federal Regulations, Parts 101 through 117. New regulations will be drafted to implement the provisions of the amendments to the VSTA. Such regulations will provide for a more comprehensive regulatory scheme, including seizure and condemnation and detention procedures. They also will establish procedures to be used in the issuance of special licenses and exemptions provided for by the legislative amendments.

Veterinary biological products are defined in the governing regulations, 9 CFR 101.2(w) as "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."

Licensing provisions for veterinary biological products and establishments are found in Part 102 of the USDA regulations (9 CFR Part 102). A product license requires the satisfactory completion of various requirements to assure purity, safety, potency, and efficacy of the products. The specific requirements were discussed in the December 31, 1984 Notice at 49 FR 50899.

Pursuant to § 103.3 (a) through (g) of the USDA regulations, a person may be authorized to ship unlicensed biological products for the purpose of evaluating experimental products by treating limited numbers of domestic animals if USDA determines that the conditions under which the experiment is to be conducted are adequate to prevent spread of disease and approves the procedures set forth in the request for such authorization (9 CFR 103.3 (a)–(g)).

Upon satisfactory completion of all requirements, including review and acceptance of labels, a U.S. Veterinary Biological Product License may be issued.

The application of new biotechnological procedures for the production of veterinary biological products is expanding constantly. For the purposes of licensing, biologics derived by recombinant DNA-techniques or developed from hybridomas, may be classified into three broad categories. This division is based upon the biological characteristics of the new products and the safety concerns they present, and is wholly analogous to the approach used in other veterinary biologics.

The first category includes inactivated recombinant DNA-derived vaccines, bacterins, bacterin-toxoids, virus subunits, or bacterial subunits. These nonviable or killed products pose no risk to the environment and present no new or unusual safety concerns. Monoclonal antibody (hybridoma) products used prophylactically, therapeutically, or as components of diagnostic kits also are included in this category.

The second category includes those products containing live microorganisms that have been modified by the addition or deletion of one or more genes. Deleted genes may code for virulence, oncogenicity, enzyme activity, or other biochemical functions. Added genes may result in the expression of new immunizing antigens or the production of novel biochemical byproducts such as beta-galactosidase. Precautions must be exercised to assure that this addition or deletion of specific genetic information does not impart increased virulence, pathogenicity, or survival advantages in these organisms which are greater than those found in natural or wild-type forms.

Modifications also must not impart undesirable new or increased adherence or invasion factors, colonization properties, or intrahost survival factors. It is important that genes added or deleted do not compromise the safety characteristics of the organisms. In most cases it is expected that they will be improved, and would therefore not pose any new threat to humans, other animal species, or to the environment.

The genetic information to be added or deleted must consist of well-characterized DNA segments. Required licensing data may include base pair analysis, sequence information, restriction endonuclease sites, as well as phenotypic characterization of the altered organism. A comparison is also required to be made between the genetically engineered organism and the wild-type form with respect to biochemical pathways, virulence traits, or other factors affecting pathogenicity.

The third category includes products using live vectors to carry recombinant-derived foreign genes that code for immunizing antigens and/or other immune stimulants. Live vectors may carry multiple recombinant-derived foreign genes since they can carry large quantities of new genetic information. They also are efficient at infecting and immunizing target animal species. These properties, for example, make vaccinia virus recombinants very popular subjects for vaccine development programs.

Live vectors currently being evaluated by licensees, applicants, and other research organizations include vaccinia, bovine papilloma virus, adenoviruses, Simian Virus–40, and yeasts. Characteristics of safety and transmission must be examined before questions and concerns dealing with

safety to humans, animals, and release into the environment can be answered and before such products can be considered for licensing.

USDA will continue to avail itself of additional expertise from the Public Health Service "Interagency Group to Monitor Vaccine Development, Production, and Usage." This interagency committee will be utilized to consider potential human health hazards from the use of veterinary biological products and to review issues such as those arising from the potential effect of organisms potentially pathogenic to people or animals.

Veterinary biological products prepared using modern biotechnological procedures such as recombinant DNA, chemical synthesis, or hybridoma technology will be treated similarly to products prepared by conventional techniques. The unlimited number and kind of products that may result from these modern biotechnology procedures make it impossible to define all requirements in specific terms. Each product is evaluated individually to determine what will be necessary to establish its purity, safety, potency, and efficacy. Scientific considerations may dictate generic areas of concerns or the use of certain tests for specific situations. Special assays, preferably using in vitro methods, may be required for potency and stability determinations. Additional tests may be required to assure safety, especially when live microorganisms are present in the biological products.

USDA is authorized to issue three types of permits for importing biological products into the United States (9 CFR 104.2). A separate United States Veterinary Biological Product permit is required for each shipment of biological product to be imported.

Permits are required for imported biological products used for research and evaluation, distribution and sale, or transit shipment only. Requests for application (U.S. Form 14–5) should be submitted to the Veterinary Biologics Staff, Veterinary Services, Animal and Plant Health Inspection Service, 6505 Belcrest Road, Hyattsville, Maryland 20782.

To provide guidance to current or prospective manufacturers employing modern biotechnological methods, the following points are presented:

1. *Recombinant DNA-Derived Products.* Genetic information coding for a product of interest and other sequences not indigenous to the host are referred to as foreign DNA. Recombinant DNA technology encompasses the isolation, characterization, and expression of foreign DNA in organisms or vectors. The specific cloned nucleotide segment coding for the desired product or other foreign DNA segments must be defined in data supporting each license application. These data must also include a description of the source of the DNA and the nucleotide sequence.

A vector is a cloning vehicle which provides a suitable origin of replication necessary for production of foreign DNA. Such replicons may be derived from plasmids, bacteriophages or viruses such as vaccina, bovine papillomavirus, adenoviruses, or SV–40.

Production of functional gene products depends on the efficient expression of cloned DNA-vector complexes in suitable host organisms. Tissue culture cells, bacteria, yeasts, and virus cells may be used as hosts for replication of vectors. The mechanisms of transfer, the copy number, and the physical state of the constructed vector inside the host cell, integrated or extrachromosomal, must be described.

USDA's licensing procedure for veterinary biological products derived from recombinant DNA involves a careful evaluation of each product on an individual basis to assure purity, safety, potency, and efficacy. Scientific and safety considerations may require specific safeguards and procedures in some situations. The USDA strongly recommends that all applicants establish Institutional Biosafety Committees which follow applicable provisions of the NIH Guidelines for Research Involving Recombinant DNA Molecules. USDA intends to propose guidelines which specifically relate to veterinary biological products. Amendments of the regulations and standards dealing with veterinary biologics will also be considered.

2. *Chemically Synthesized Antigens.* When the product consists of chemically synthesized polypetides, the appropriate amino acid sequences will mimic the antigenic site or epitope found in the native antigen where one exists. Procedures used to increase or prolong an immune response, such as coupling to carrier proteins or addition of adjuvants, must also be described. Immunological data derived from chemically synthesized peptides must be as definitive as those from natural antigens.

3. *Monoclonal Antibody Products.* The specificity and potency of monoclonal antibody will be compared with those of similar polyclonal antibody products where appropriate. The sensitivity and specificity of monoclonal antibody products used in diagnostic test kits and their potency characteristics when used therapeutically must be similar to conventional antibody. Monoclonal antibody must be derived from Master Cell Stocks which meet the applicable requirements of 9 CFR 113.52. In addition, as is currently required, a description of cell cloning procedures, preparation, and characterization of cell passages must also be provided.

The Outline of Production must describe all processes including scale-up, ascites fluid or cell culture supernatant preparation, purification, concentration, and inactivation. Mouse colonies must be screened to demonstrate freedom from adventitious agents, especially those detected by the mouse antibody production (MAP) test. If the MAP test discloses the presence of adventitious agents, the product shall not be released unless inactivation procedures approved by Veterinary Services have been performed and tests conducted to ensure proper application of the procedures.

4. *Master Seeds.* Bacterial or viral seed stocks used to prepare veterinary biological products must meet established procedures used to certify Master Seeds for biological products.

The Master Seed for recombinant DNA-derived products may consist of a plasmid or virus carrying the inserted gene. This constructed plasmid is then introduced into the appropriate eukaryotic or prokaryotic expression system selected for vaccine production. Genomic DNA may also be transfected directly into a variety of mammalian cells. Alternatively, in such cases, the stable transfected cell could be considered as the Master Seed.

The establishment of Master Seeds consisting of constructed plasmids or transfected cells requires submission of background information concerning the recombinant DNA procedures used to isolate, purify, and identify genetic material from one source and the modification used for inserting of this material into a new host. Data from cloning, isolation, proliferation, and selection of genetically unique cells would be retained by licensed applicants. In order to characterize adequately the foreign DNA used to code for a particular antigen, the manufacturer must provide a nucleotide sequence analysis.

Tissue culture-propagated cells from vertebrate animals used for vector propagation and antigen production must meet the requirements of 9 CFR 113.51 or 113.52.

If a Master Seed has been accepted by Veterinary Services for use in a licensed product, further genetic modifications may be approved with reduced

requirements for additional host animal efficacy studies.

Each Outline of Production must be prepared in accordance with 9 CFR 114.9. Outlines must include procedures to ensure consistency in production and recovery of specific antigenic material. Recovery procedures must include removal of excessive antibiotic levels (9 CFR 114.10) and undesirable fermentation byproducts such as excessive levels of bacterial endotoxins. Serial release tests for purity, safety, and potency will be required. In addition product characterization tests may be required to demonstrate consistent gene expression.

Organisms and Vectors

Pursuant to the Act of February 2, 1903, (21 U.S.C. 111), and the VSTA, USDA has authority to issue such regulations and take such measures as may be deemed proper to prevent the introduction or dissemination into the United States of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry from a foreign country into the United States or from one State or territory of the United States or the District of Columbia to another. The importation into the United States or interstate shipment of organisms and vectors is regulated under 9 CFR Part 122. Organisms and vectors are defined in 9 CFR 122.1 as entities which may introduce or disseminate any contagious or infectious disease of animals. Such substances may not be shipped interstate or imported without a permit. Permit applications must completely describe the substances, intended use, location of the permittee, and safeguards.

A number of revised administrative and technical provisions have been instituted to expedite the USDA review and issuance of permits for importation or organisms and vectors which include cell cultures and hybridomas. No animal-origin biological materials, such as cell cultures, monoclonal antibodies, organisms, vectors, or related material, may be imported into the United States without a Veterinary Services (VS) Permit (VS Form 16–3A). To obtain a permit, an application (VS Form 16–3) should be submitted to: Import-Export Staff, Organisms and Vectors, VS, APHIS, USDA, 6505 Belcrest Road, Hyattsville, MD 20782. This is different from the permit required to import veterinary biologics pursuant to Part 104 of the USDA regulations governing such products (VS Form 14–5 and 14–6).

Applicants must also complete the questionnaire entitled "Importation Information" and submit it with their application. Based upon the information submitted by the applicant, a determination will be made if the material to be imported requires safety testing to ensure it is free from livestock pathogens. Safety testing is conducted at the Foreign Animal Disease Diagnostic Laboratory (FADDL), Plum Island, New York.

Applicants will be advised if a safety test is required and will be given an estimate of the cost for conducting the test. Applicants desiring to have material safety tested must enter into a Cooperative Trust Fund Agreement with APHIS, VS, and deposit in advance sufficient funds to cover the estimated cost. The Import-Export Animals and Products Staff will initiate the Cooperative Trust Fund Agreement. In order to expedite the procedure, VS may issue a permit for the material to be shipped to FADDL pending receipt of the funds and Cooperative Trust Fund Agreement. However, the signed Cooperative Agreement, plus the necessary funds, must be received by VS before testing can be scheduled at FADDL.

Usually 60 to 90 days is needed for issuing a permit for importing material to Plum Island, New York, the completion of safety tests, and the transfer of the imported material to the applicant. A minimum of four vials, each containing at least 1 million cells from a uniform lot, is required for the safety testing.

When the test is completed and a determination made that the imported material is free from livestock pathogens, the remainder of the imported material is released directly to the importer under conditions specified in the permit.

If an importer wishes to import cell cultures and/or hybridoma cells on a regular basis, the applicant may enter into a continuous Cooperative Trust Fund Agreement with VS and establish an escrow account to ensure that unnecessary delays will not occur due to insufficent funds.

Each safety test utilizing susceptible host animals usually cost approximately $2,000 to $3,000. Sometimes it is possible to reduce the cost by pooling samples in one host animal test. Scientists at FADDL developed in vitro safety tests to detect certain livestock pathogens resulting in substantial cost savings for importers. The current cost of each in vitro test is approximately $500, depending upon the type of animal disease present in the country of origin as well as the intended use of the imported material.

Safety testing may not be required for some cell cultures imported for human diagnostic purposes and research. Examples of material which could enter without safety testing include cultured human bone marrow cells, amniocentesis samples, and cells imported for karyotype analysis. Applications for such cell cultures will be considered individually.

Permit applications are evaluated by a new classification scheme that correlates intended use of imported cell cultures with the level of safety testing conducted at FADDL.

The following classification of cell cultures is based on intended use and generally indicates the level of safety testing required.

Class I Cell cultures to be used for the production of products such as vaccines, hormones, or other biologicals to be used in livestock, poultry, or for commercial distribution.

Requirement: These cell cultures must be safety tested at FADDL using susceptible host animals, approved in vitro test, and/or laboratory animals.

Class II Cell cultures to be used only for in vitro studies and not to be used in animals other than primates.

Requirement: These cultures may not require safety testing. The material may be sent directly to the importer when no safety testing is required. The permit (VS Form 16–3A) will specify restrictions such as "FOR IN VITRO LABORATORY TESTS: DO NOT INOCULATE INTO LIVESTOCK, BIRDS, OR LABORATORY ANIMALS."

Cell cultures imported under permit which do not require a safety test may not be distributed to other laboratories without prior approval from USDA, APHIS, VS. Applications for the distribution of imported material should be submitted to the USDA, APHIS, VS, Import-Export Staff, Organisms and Vectors.

When appropriate, a review is conducted by the Administrator's Parent Committee on Organisms and Vectors. Members of this committee have wide expertise in evaluating safety. Clearance may also require testing in high security facilities at the Veterinary Services, FADDL, Plum Island, New York.

B. Plants and Plant Products

Pursuant to the authority granted by the Federal Plant Pest Act (FPPA) of May 23, 1957, as amended (7 U.S.C. 150 aa through 150 jj), and the Plant Quarantine Act (PQA) of August 20, 1912, as amended (7 U.S.C. 151 through 164, 166, and 167), USDA has regulatory authority over the movement into or within and through the United States of

plants, plant products, plant pests, and any product or article which may contain a plant pest at the time of movement. These articles are regulated in order to prevent the introduction, spread, or establishment of plant pests new to or not widely prevalent in the United States. The regulations implementing this statutory authority are found in 7 CFR Parts 300 through 399.

"Plant Pest," as defined by statute, means any living stage of any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, or 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 (7 U.S.C. 150aa(c)).

"Movement," as defined by statute, means to ship, deposit for transmission in the mail, otherwise offer for shipment, offer for entry, import, receive for transportation, carry, or otherwise transport or move, or allow to be moved, by mail or otherwise (7 U.S.C. 150aa(g)).

The current permit system requirements for the movement into or within and through the United States of plants, plant products, plant pests, and other articles regulated by FPPA and PQA were fully described in the December 31, 1984 Notice at 49 FR 50900–01. The procedures for issuing permits for the movement of plant pests were discussed separately from plants, plant products and other articles which may contain plant pests at 49 FR 50901–02. USDA regulates the importation of noxious weeds through a permit system similar to that established for plant pests. The existing regulations in 7 CFR Part 360 which designate plants as noxious weeds and establish procedures for obtaining an import permit were described at 49 FR 50902.

Regulation of the Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are or Which There Is Reason to Believe Are Plant Pests

The FPPA and PQA are applicable to the movement of plants, plant products, and other articles and plant pests developed through genetic engineering if such plants, plant products, other articles, or plant pests present a risk of plant pest introduction, spread, or establishment.

Under the authority granted by the FPPA and PQA, USDA is proposing new regulations which would impose restrictions on 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.

In accordance with the provisions of the FPPA and PQA, USDA must determine the plant pest status of plants, plant products or articles to be moved into or within or through the United States. The evaluation process for determining what safeguards, if any, can be imposed which would allow the movement of the plant pest without risk that the plant pest would be disseminated were described in the December 31, 1984 Notice at 49 FR 50901–02. For genetically engineered material from dissimilar source organisms (inter-generic combinations), the determination may be complex. Information about genetically engineered organisms produced through the use of donor, vector/vector agent and recipient organisms that are from a list of known plant pests is needed in order that such organisms be properly regulated.

During the past year, USDA has received permit applications to move genetically engineered organisms into or through the United States. USDA is confident that organisms altered through genetic engineering will play a major role in increased plant yield and improved plant quality. However, a genetically engineered organism derived from organisms that are plant pests also presents a risk of plant pest introduction. The organisms themselves, the cultures in which they are transported, or their packaging may be contaminated with plant pathogens. Genetic alteration may create a plant pest new to and not widespread in the United States. It is necessary, therefore, to establish appropriate safeguards to prevent the introduction of genetically engineered organisms that pose a threat to agriculture. Other genetically engineered organisms that are not plant pests or where there is no reason to believe such organisms are plant pests would not be regulated.

New data have to be required in order to properly evaluate permit applications for those organisms which are plant pests or which there is reason to believe are plant pests. A determination was made that additional data requirements would be incorporated into proposed regulations for those genetically engineered organisms which are of concern under the provisions of the FPPA and PQA.

USDA is publishing as a companion document in the "proposed rules section" of this issue of the Federal Register its proposed regulations pertaining to organisms and products altered or produced through genetic engineering which are on plant pests or which there is reason to believe are plant pests.

The proposed regulations would establish a new part entitled, "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", in Title 7 of the Code of Regulations (7 CFR), pursuant to the authority of the FFPA, as amended (7 U.S.C. 150aa–150jj) and the PQA, as amended, (7 U.S.C. 151–164, 166, 167). Such proposed regulations would regulate the importation into and movement within and through the United States as well as prevent the release into the environment of certain organisms, or products altered or produced through genetic engineering, which are plant pests or which there is reason to believe are plant pests.

The proposed regulations would restrict the "introduction" of certain organisms and products altered or produced through genetic engineering, referred to as "regulated articles." In this context, "introduction" means to move into the United States, to release into the environment, or to move interstate, or any attempt thereat." "Release into the environment" means "use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or fermenter or other contained structure."

USDA's proposed regulations, which are designed to prevent the release into the environment of genetically engineered organisms which are plant pests or which there is reason to believe are plant pests are consistent with the legislative intent of the FPPA. The FPPA was enacted in 1957 and was intended as "gap filling" legislation for the purpose of protecting American agriculture against invasion by plant pests and diseases which are new to or not theretofore known to be widely prevalent or distributed within and throughout the United States. The FPPA also provides USDA with authority to regulate insects or pests that might later be found to be injurious to cultivated crops. The release into the environment of a genetically engineered plant pest is tantamount to the introduction of a plant pest which is new to and not theretofore known to be widely prevalent within and throughout the United States and subject to regulation under the FPPA.

It should be noted that "regulated article" would be defined as any organism or product altered or produced through genetic engineering, if the donor

organism, recipient organism, or vector or vector agent belongs to a group of organisms designated by the proposed regulations as having plant pests or any organism or product which USDA determines is a plant pest or which there is reason to believe is a plant pest. Under USDA's proposed definition, certain microorganisms would be excluded if the recipient microorganism is non-pathogenic, is non-infectious, and otherwise not a plant pest, and resulted from the addition of genetic material that is well characterized and contains only non-coding regulatory regions. Restrictions would be required for regulated articles because they are plant pests, or because USDA has reason to believe they are plant pests. The proposed regulations would require that a person obtain a permit prior to the introduction of a regulated article and would list specific conditions required for the introduction of a regulated article. The regulated article could be introduced only if all conditions in the proposed regulations as well as all conditions specified on the permit were met. It is important to note that in considering whether a permit can be issued for the introduction of a genetically engineered organism, USDA will perform the same comprehensive analysis that is used in determining whether a permit can be issued for the movement of a "conventional" plant pest. Such asessment shall include an examination of the factors that were discussed in the December 31, 1984, Notice at 49 FR 50901–02 as part of the evaluation process for determining what safeguards can be imposed which would allow the movement of a plant pest without risk of dissemination. These factors are oriented toward an examination of the ecological and environmental effects of a release of the genetically engineered organism or product into the environment.

The proposed regulations also contain provisions for a certificate of exemption for those organisms or products altered or produced through genetic engineering that are not subject to the proposed regulations. A person seeking to introduce an exempt article could voluntarily request a certificate of exemption to facilitate the introduction of the organism or product.

The proposed regulations provide a list of groups of organisms which are plant pests or contain plant pests. If the donor, vector/vector agent, or recipient of the genetically engineered organism is derived from an organism on the list of organisms containing plant pests, such genetically engineered organism would be deemed a "regulated article".

As defined in the proposed regulations, a plant pest includes microorganisms such as bacteria and viruses, and thus a "regulated article" may be a microorganism unless it meets the provisions for exclusion. It is important to note that in some instances certain microorganisms will be subject to joint regulation by USDA and EPA. USDA has jurisdication over certain microorganisms under the FPPA and PQA if the microorganisms are a plant pest. EPA would have jurisdiction under the Toxic Substances Control Act (TSCA) if the microorganism is deemed to be a "new" microorganism or under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended (FIFRA) if the microorginism is to be used as a pesticide. Because each Agency has a different statutory mandate, certain jurisdictional overlaps cannot be avoided. However, EPA and USDA will work cooperatively and simultaneously in the evaluation of genetically engineered microorganisms that fall under the jurisdication of both Agencies. To expedite the review of these microorganisms each Agency will appoint contact persons to coordinate the review to ensure data requests are not duplicated.

The specifics of which microorganisms will be subject to dual Agency review, or primarily single Agency review, is set forth in the preamble of USDA's proposed regulations being published as a companion document to this policy statement. That document should be consulted for further information.

A key to determining whether a genetically engineered organism will be regulated by USDA is the list of organisms containing plant pests that appears in § 340.2 in proposed Part 340. USDA acknowledges that this is not an exhaustive list, and that it does not attempt to list every pest species. Comments are welcome on the list as well as on other parts of the proposed regulations.

In order to solicit as many comments as possible on the list and all other parts of the proposed regulations, USDA has scheduled public hearings in Washington, DC and Sacramento, California, during the 60-day comment period. The time and place of the public hearings as well as the address to send written comments is specified in the preamble to the proposed regulations.

USDA believes that through the submission of detailed comments and full participation by public and private interests, USDA will be able to promulgate a final regulation that will prevent the introduction and dissemination of genetically engineered organisms which are plant pests or which there is reason to believe are plant pests, yet not impede the development of biotechnology.

C. Meat and Poultry Products

The Food and Safety Inspection Service (FSIS) is responsible for assuring the safety, wholesomeness, and proper labeling of food products prepared from domestic livestock and poultry. The Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA) require FSIS to inspect cattle, sheep, swine, goats, equines, poultry, and food products prepared from them which are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled, marked, and packaged. Inspection under these statutes is mandatory. The cost of inspection, except for overtime and holiday inspection work, is required to be borne by the USDA. Food, animals and animal products, other than those required to be inspected under the FMIA and PPIA, may be inspected under a voluntary, reimbursable inspection program established under the Agricultural Marketing Act of 1946.

Within the framework of food safety statutes, FSIS has developed regulations for research on animals that are administered experimental animal drugs, biologics, and pesticides (9 CFR 309.17 and 381.75). These regulations state that no animal used in any research investigation involving an experimental biological product, drug, or chemical shall be eligible for slaughter at an official establishment unless certain conditions are met. These conditions include any of several different ways of demonstrating that the use of such biological product, drug, or chemical will not result in the products of such animals being adulterated.

Products Subject to Review. FSIS anticipates that many food animals which are subject to the new techniques of modern biotechnology will not differ substantially in appearance, behavior, or general health from currently inspected cattle, sheep, swine, goats, equines, and poultry. They would be subject to the same inspection procedures and regulations as tradionally inspected food animals. FSIS is aware that some genetically engineered animals, such as mosaics, chimeras, and some hybrids, may differ substantially from animals that are inspected currently under the FMIA and PPIA. If such animals are ever intended for use as human food and are presented for inspection at an official

establishment, a decision would have to be made as to whether such animals were covered under the FMIA or PPIA, and if not, whether the FMIA and PPIA should be amended to require inspection of such animals and their products.

Implementation of Review Authority. FSIS's approach toward the review of food animals resulting from the techniques of moderm biotechnology consists, in general, of two phases. The first, an experimental phase, focuses on the experimental aspects of vector administration, gene transfer and gene expression. Since artificial vectors used in animal gene transfer may be considered as either animals drugs or animal biologics, their administration to food animals would be covered under the current regulations on animals used for research (9 CFR 309.17 and 381.75). The requirement that an animal carcass intended for use as human food not be adulterated may require that certain phenotypic, biochemical, and microbiological parameters not be exceeded before the animal can be slaughered for human food. Depending on future developments, FSIS may amend the regulations (9 CFR 309.17 and 381.75) to provide further assurance that the products of animals genetically engineered by certain techniques are not adulterated. The second phase would be carried out under existing regulations (9 CFR Parts 301 through 381) and would focus on the commercial development, production, inspection and labeling of food animals and food animal products.

D. Seeds

The Federal Seed Act (FSA) (7 U.S.C. 1551 *et seq.*) defines USDA regulatory authority over the importation and interstate shipment of agricultural and vegetable seeds. It does not apply to the production or intrastate distribution of seeds or to seeds other than agricultural or vegetable seeds ("agricultrual seeds" are grass, forage, and field crop seeds).

The FSA prohibits interstate shipment of seed that contains noxious weed seeds at levels in violation of the laws of the State of destination or in excess of levels allowed by the Secretary of Agriculture. This provision applies primarily to seed adulterated with noxious weed seed. In a few instances, however, States have determined that a particular variety of agricultural or vegetable seed is itself a noxious weed. In these instances, FSA prohibits the interstate shipment of the seed into those States. The FSA also allows the Secretary to prohibit the importation of agricultural and vegetable seed which is adulterated with noxious weed seed or which is unfit for seeding purposes.

The authority granted to the Secretary by the FSA to prohibit the interstate shipment or importation of seeds which are found to be detrimental to the agricutural interests of the United States applies to seeds genetically engineered with the modern biotechnology to the same extent as any other seeds.

V. Scientific Review Mechanisms

The manner in which both regulation and oversight of research in agriculture-related biotechnology evolves and is implemented in the United States will have a direct impact on the competitiveness of U.S. industry in both domestic and world markets. Inconsistent or unnecessary procedures for regulation and research will place the U.S. scientific effort and U.S. producers at a substantial disadvantage. It also is important that safeguards be built into biotechnological research processes, and that releases be based on careful evaluations while further experience is being gained. Therefore, USDA feels that such regulatory and research decisions must be based on the best science available.

While the responsibilities within USDA for biotechnology reside with the Assistant Secretary for Science and Education and the Assistant Secretary for Marketing and Inspection Services as the delegates of the Secretary of Agriculture, in carrying out their respective responsibilities based on the best science available, they would be able to take advantage of the expertise and perspectives within the Federal Government through a committee to be called the Committee on Biotechnology in Agriculture (CBA). The CBA, to be chaired by these two Assistant Secretaries, will function both as a policy body in the USDA and a bridge between its research and regulating structures.

Committee on Biotechnology in Agriculture

The objectives of the CBA will include:

—To provide advice, when requested, on initiatives, proposals, and policy for agriculture-related regulation and research, and assist in the coordination of these activities;
—To review scientific issues submitted by agencies within the Department;
—To assist in identifying data gaps for basic research in agricultural biotechnology;
—To foster public awareness of the scientific issues in biotechnology;
—To provide Departmental support for participation in the FCCSET BSCC.

USDA expects that the CBA also will utilize existing cooperative entities (e.g., other Federal agencies, universities, State regulatory officials, the public sector, and industry) to acquire, when necessary, information for addressing those issues submitted to it. Such entities, when requested, can provide technical support for sound regulatory and research decisions regarding the use of biotechnology in agriculture and foresty. These entities offer a vast scientific resource upon which USDA can draw.

VI. Summary of Comments

USDA received the comments of one hundred-two (102) respondents, one-half of whom commented specifically on the USDA policy statement. Although USDA agencies considered all comments on the coordinated policy proposal, this response is confined to comments on the USDA portion of the notice.

The two largest categories of respondents were business and academic, followed closely by associations representing these interests. Comments came in lesser numbers from environmental and public interest groups, individuals, law firms, and foreign governments, as well as the National Institutes of Health Recombinant DNA Advisory Committee (NIH-RAC) and a member of the U.S. Congress

The USDA response to the comments follows the form of the original notice, with a discussion of comments on regulatory philosophy followed by a response to comments on the regulatory framework.

Comments on the Noture of Products of Modern Biotechnology: Fourteen respondents stressed their agreement with the USDA statement that "agriculture and forestry products developed by modern biotechnology will not differ fundamentally from conventional products," while six commenters dissented. Three respondents felt that genetic engineering across species barriers did create a potentially different product and the possiblity of unique ecological effects. Concern about the "need for public trust" and public assurance on safety and ethical issues was stressed by three commenters. Seven respondents agreed with USDA that "to date, no unique or safety problems have been associated with products of genetic engineering," but four of the same commenters who view biotechnology products as fundamentally different from conventional products stressed that the potential exists for safety problems with biotechnology applications.

Response: USDA recognizes the importance of ecological effects and the need for developing procedures responsive to public concerns about safety.

Although USDA's regulatory philosophy remains as stated, additions to regulatory procedures are being proposed for genetically engineered plants and plant products and veterinary biologics produced by biotechnology (see section IV). The previously discussed delegations of authority within USDA for biotechnology increase the effectiveness of the administration of current and proposed regulatory procedures affecting the products of modern biotechnology.

For veterinary biological products, USDA is currently developing additional procedures pursuant to the VSTA, as amended, for evaluating requests to conduct experimental field trials with live vectors containing genetically engineered organisms or to support product license applications. The procedures being developed consider the parental organism and the effect of the gene alteration on the genetic properties of the recipient, especially the survival, reproduction, and dispersal characteristics. A careful analysis of the genetics, biology, and ecology of the wild-type and modified microorganisms will provide as reasonable prediction of the risks which might be associated with use of the altered organisms.

USDA is proposing regulations pursuant to the Federal Plant Pest Act (FPPA) and the Plant Quarantine Act (PQA) for regulating the introduction of certain organisms of products thereof altered or produced through biotechnology which are plant pests or may become plant pests. This proposed rule should assist USDA in assessing the ecological effects of the release of such genetically engineered organisms into the environment.

Guidelines for oversight of agricultural biotechnology research funded by USDA will be issued under the authority of the Food Security Act of 1985.

USDA also is establishing scientific review mechanisms to assist in research and regulatory decisions (see section V).

These proposed modifications in the procedural framework are described as a part of the final policy statement for veterinary biologics, plants and plant products, research, and scientific review mechanisms.

Comments of the Adequacy of Existing Authority: Thirteen commenters agreed with USDA that its existing regulatory framework is adequate for biotechnology applications, and nine favor the case-by-case approach under existing authority. Five commenters felt that new legislation is or may be needed; two of the five oppose the case-by-case approach.

Response: USDA has examined its statutory authority for regulating biotechnology products and processes, and USDA agencies have processed licensing and permit applications under the existing statutes. The existing authority is considered adequate at this time. Established procedures, with the proposed modifications, can be adapted effectively to handle biotechnology applications. USDA is currently considering genetic engineering applications on a case-by-case basis using existing authority.

Comments on Need for Procedures and Guidelines: Sixteen respondents commented that USDA had not outlined procedures for the review and approval of genetically engineered products. Twelve respondents stressed the need for flexibility, and six requested sunset provisions in USDA biotechnology regulations.

Response: The USDA policy statement of December 31, 1984, did outline procedures currently used for the review and approval of certain genetically engineered products. In considering license applications for genetically engineered veterinary biologics, USDA follows the standards and procedures applicable to all such products found in §§ 101–117 of the applicable regulations and standards (9 CFR 101–117). In the December 31, 1984 Notice, USDA offered supplementary guidelines for licensing such products. New procedures are being developed to evaluate production and testing of veterinary biologics derived through use of genetic engineering techniques. The information needed for proper evaluation will depend on the parent organism and the effect of the gene alteration on the genetic properties of the recipient. A paper describing the USDA licensing policy for biologics produced by recombinant DNA technology was presented at the Joint International Association of Biological Standardization/World Health Organization Symposium on "Standardization and Control of Biologics Produced by Recombinant DNA Technology," Geneva, Switzerland, 1983 (published in *Developments in Biological Standardization*, V. 59, pp. 167–173, S. Korgel, Basel, 1985). The paper describes requirements for plasmid/vector characterization and stability, and correlation to conventional Master Seed concepts, as well as methodology which can be used to monitor antigenic expression, concentration, purification, and stability testing during production and recovery.

The movement of genetically engineered products which are plant pests and present a risk of plant pest introduction or spread is regulated by 7 CFR 330.200 implemented pursuant to the FPPA and PQA. The movement of organisms and vectors which may cause desease in animals is regulated under 9 CFR Part 122.

USDA realized that the statement left unanswered some questions about the means for review and approval of various genetically engineered products. The proposed regulations described in section IV(B), implemented under the authority of the FPPA establish permit requirements for the "introduction" of organisms altered or produced by genetic engineering which are or may become plant pests. The regulations would be flexible because organisms determined not to be plant pests would be exempt, and this category could be expanded in the future to include organisms whose plant pest status is currently uncertain and therefore restricted. It is hoped that the discussion in section IV(B) of this policy statement answers any remaining questions about the review and approval procedures for such genetically engineered products.

Comments on Confidential Business Information (CBI): Six commenters representing business and scientific interests expressed concern about the protection of "confidential business information" in the USDA regulatory process while two public interest groups stressed the "public's right to know."

Response: The USDA regulations implementing the Freedom of Information Act (FOIA) (5 U.S.C. 552) are found in 7 CFR 1.1–1.16. The FOIA provides that Federal agencies must make available to the public all records not specifically exempt from disclosure. Exemptions include "trade secrets and commercial or financial information," (5 U.S.C. 552(b)(4)). On September 23, 1985, USDA's APHIS issued a policy statement on the protection of privileged or confidential information (50 FR 38561–38563). This policy statement establishes requirements for the control and protection of documents received by APHIS that contain privileged or confidential business information concerning biotechnology and the veterinary biologics program. The procedures established conform to the FOIA requirements for both protection and disclosure.

Comments on Use of NIH Guidelines: Four respondents questioned the USDA requirements that manufacturers of

veterinary biological products using recombinant DNA technology follow the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). One respondent thought USDA implied that all people "who work with recombinant DNA plants" would be required to comply with the NIH Guidelines, and requested procedural guidelines for industry.

Response: The USDA does not require that the manufacturers of veterinary biological products or plant products of recombinant DNA technology follow the NIH Guidelines. However, USDA strongly recommends that all license applicants for veterinary biologics follow appropriate provisions of the NIH Guidelines, such as those regarding the establishment of an institutional biosafety committee. USDA intends to propose guidelines that will parallel closely the NIH Guidelines, and it intends to recommend strongly that entities not required to follow the USDA guidelines do so voluntarily.

Comments on Importation of Cell-Lines: Three associations representing biotechnology companies requested that USDA take steps to reduce delays in the clearance and testing procedures required for the importation of biotechnology-derived products and cell-lines. On February 12, 1985, the Association of Biotechnology Companies (ABC) delivered a report on USDA importation guarantine issues to the APHIS Parent Committee for Foreign Pathogens and Vectors. This report was an attachment to the ABC comment letter.

Response: The USDA has instituted a number of revised administrative and technical provisions to expedite the issuance of permits for importation of organisms and vectors which include cell cultures and hybridomas. A supplementary questionnaire, designed to insure adequate information on cell cultures and products from recombinant DNA or hybridoma technologies, now accompanies each permit application. Applicants are advised whether or not a safety test is required and a cost estimate is given. Safety testing may be conducted concurrently with the administrative review of the permit application, but only at APHIS' Foreign Animal Disease Diagnostic Laboratory (FADDL) at Plum Island, New York. New test procedures have reduced the cost of safety testing, and the cost per sample can be further reduced by conducting a safety test with pooled samples. Permit applications are evaluated using a new classification scheme that equates intended use of imported cell cultures with the level of safety testing required at FADDL. Class I cell cultures, employed in the preparation of products such as enzymes, vaccines, or hormones for commercial use, are subject to complete safety testing. Class II cell cultures, used only for in vitro studies and not to be used in animals other than primates, are subject to a lesser degree of testing.

Comments on Risk Analysis: Seven respondents discussed the issue of risk assessment or risk/benefit analysis of biotechnology applications. Comments varied from a recommendation that "standard risk assessment methodologies" be adopted by all agencies to a warning against attempting to regulate the "hypothetical and imaginary "potential' dangers" of recombinant DNA techniques.

Response: The National Environmental Policy Act (NEPA) applies to USDA actions. The "APHIS Guidelines Concerning Implementation of NEPA Procedures" (44 FR 50381, August 28, 1979) would be used to make an environmental assessment or environmental impact statement of the effects of a proposed release of a genetically engineered organism regulated pursuant to the VSTA, the FPPA and PQA, and related statutes. A formal risk management procedure based on a wide variety of safety concepts will be used to evaluate systematically proposed releases. The information required by any new regulations promulgated under the FPPA and PQA would be used to prepare the environmental assessment for release of a genetically engineered product which is a plant pest or may become a plant pest.

In normal husbandry and laboratory practices, veterinary biological products normally are not considered to be released into the environment. In the event that a conventionally prepared or recombinant derived product would be considered to be released into the environment, the issuance of a license or import permit would require compliance with procedures being developed and interagency approval. The procedures under development consider the parental organism and the effect on the gene alteration on the genetic properties of the recipient, especially the survival, reproduction and dispersal characteristics.

Safety, ethics, and policy issues in agricultural biotechnology research will be overseen by the Committee on Biotechnology in Agriculture (CBA) and such supporting technical advisory groups as may be established by the USDA agencies. Currently, all USDA and USDA-sponsored research involving recombinant DNA must be cleared prior to initiation for compliance with the NIH Guidelines.

Comments on Jurisdiction: The potential for overlapping jurisdiction in the policy notice drew the largest number of comments. Eighteen respondents pointed out that both USDA and EPA propose to regulate agricultural microorganisms. Respondents representing the interests of the veterinary biologics industry contended that a jurisdictional dispute between USDA and FDA delayed the approval of bovine interferon. While generally supporting the concept of the memorandum of understanding (MOU) between USDA and FDA to resolve jurisdictional disputes, one respondent challenged the legality of the MOU, noting that it contains the statement that "animal biological products generally act through a specific immune process," while USDA's current regulations do not restrict its jurisdiction to products operating through such a mechanism of action. Industry respondents also pointed out that the intrastate producer of veterinary biologics is not regulated by USDA. Two firms and one industry association urged prompt Federal oversight action so that States do not act independently to regulate biotechnology products.

Response: USDA agrees that there is the potential for overlapping jurisdiction among the Federal agencies involved in regulating biotechnology products. USDA and EPA representatives have discussed jurisdiction over genetic engineering applications since 1983. USDA and EPA have begun to establish a regulatory procedure for reviewing certain submissions of genetically engineered microorganism applications, a procedure which has resulted in joint consultation on several proposals for release into the environment of organisms altered by genetic engineering.

For veterinary biologics regulated under the VSTA, use of procedures currently under development will increase USDA effectiveness in evaluating biotechnology license and product applications. The MOU between USDA and FDA was published on June 8, 1982, in an attempt to resolve the issue of new products which fall into the questionable definitional area between animal drugs regulated by FDA and animal biologics regulated by USDA. An interpretation by some that the term animal biologics only includes substances that act through a specific immune process has resulted in some confusion. There is nothing in USDA's

current regulations or law which restricts its jurisdiction to products acting solely through this mechanism of action, and because of this fact, the memorandum qualifies its reference to specific immune process by the word "generally." Although efforts will be made to clarify the issue further, it should be noted that there appears to be little uncertainty about whether a particular product is a veterinary drug or biologic.

The Food Security Act of 1985 contains amendments to the VSTA that extend USDA's jurisdiction to veterinary biologics which are shipped intrastate or exported. The provisions of the amendments are discussed more fully in Section IV.

Comments on the National Biological Impact Assessment Program (NBIAP): Seven respondents commented on the NBIAP, the proposal by the National Association of State Universities and Land Grant Colleges (NASULGC) for establishing a program to assess genetically engineered organisms before they are released into the environment. Three commenters—a member of Congress, a spokesperson for a biotechnology firm, and an officer of an environmental organization—posed questions about the proposal. The questions concerned the NBIAP's statutory or regulatory status; its relation to other USDA agency operations and other Federal agency operations; the processes of risk assessment to be used; its adequacy to review an increasing volume of products; and the appropriateness of biohazard committees as vehicles for review of commercial processes and products. Four respondents representing NASULGC institutions endorsed the proposal stating the view that the agricultural research community has the capability to develop guidelines and assess impacts of biotechnology research and commercial products. The major goal of the program was thought to be insuring the safety of society and the environment.

Response: NBIAP is a scientific advisory system that would be available to the Assistant Secretary for Science and Education. By this system the USDA can draw upon the best experience available from scientists in universities, Federal laboratories, and industry to help assess the risks involved in the processes and products from RDNA work in biotechnology.

NBIAP shall act in an advisory capacity and is in no direct way a part of the formal approval process. It is available to provide assessment, but is not a mandatory process.

Comments on Definitions, Terms, and Data Requirements: Five respondents recommended changes in the definitions, terms, data requirements or classification used by USDA in the notice. Each recommendation is discussed below.

Two respondents commented on the USDA statement of licensing policy for veterinary biologics produced by modern biotechnical methods at 49 FR 50899–50900. Under the heading "1. Recombinant DNA-Derived Products," a manufacturer of veterinary biologics questioned the need to provide the entire nucleotide sequence of a foreign DNA being cloned into a vector.

It is USDA's position that in order to characterize adequately the foreign DNA used to code a particular antigen, the manufacturer should provide a nucleotide sequence analysis. The construction of the vector used for expression of the cloned nucleotide sequence also should include source and function of the component parts of the vector, i.e., origin of replication, antibiotic resistance genes, promotor, enhancers, etc. The manufacturer also questioned the data requirement under the heading "2. Chemically Synthesized Antigens" concerning the persistence of the immune response following administration of the synthetic peptide. The USDA feels that a major concern with the use of synthetic peptides is the development persistence of the immune response. USDA does not intend to require more stringent efficacy data than that necessary to support a veterinary biologic license application employing natural antigens. However, immunological data derived from chemically synthesized peptides must be as definitive as the serological response from natural or nonsynthetic antigens. With respect to the next sentence in the policy statement, an individual respondent proposed a change from the term "antibody response" to "immune response." It is true that the term used in the sentence "Procedures used to increase or prolong an antibody response . . ." is somewhat limiting and can create confusion between B-cell and T-cell response. Therefore, the recommendation to replace "antibody response" with the term "immune response" is accepted, since both T-cell responses as well as T-cell/B-cell interactions would be included in the statement.

On the subject of plants and plant pests, a plant pathologist commented on the references to *Pseudomonas syringae* as plant pathogens under the heading "ice nucleation negative bacteria" at 49 FR 50902. The respondent noted that none of the strains of *Pseudomonas syringae* currently proposed for use are plant pathogens and that it would be more correct to call *P. syringae* plant-associated bacteria, some of which are pathogens. USDA will clarify future references to these organisms as the respondent suggests. According to current practice, and under the proposed FPPA regulations, an applicant for a USDA permit to import or move *Pseudomonas syringae* would be required to submit data to show whether or not the strain was a plant pest.

Addendum—Research Legislative Authorities

The USDA is authorized under its Organic Act (7 U.S.C. 2201 et seq.) and other legislation to conduct and support research in wide ranging areas of agriculture. Examples of such other laws include:

The Alcohol Fuels Research (7 U.S.C. 3154); the National Latex Commercialization and and Economic Development Act (7 U.S.C. 178–178n); the Animal Health and Disease Research Act (7 U.S.C. 3195); Special Research Grants (7 U.S.C. 450i(c)); The National Aquaculture Act (16 U.S.C. 2801 et seq.); the Cotton Research and Promotion Act (7 U.S.C. 2101 et seq.); the Potato Research Information Act (7 U.S.C. 2611–2627); the Egg Research and Consumer Information Act (7 U.S.C. 701 et seq.); the Beef Research and Information Act (7 U.S.C. 2901 et seq.); the Wheat and Wheat Foods Research and Nutrition Education Act (7 U.S.C. 3401 et seq.); the Animal Cancer Research Act (7 U.S.C. 3901 et seq.); the Floral Research and Consumer Information Act (7 U.S.C. 4301 et seq.); and the Forest Research Assistance Act (16 U.S.C. 582a–582a–7).

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

Agency Guidelines on Biotechnology

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Announcement of guidelines on occupational safety and health in the field of biotechnology.

SUMMARY: OSHA has reviewed its responsibilities under the Occupational Safety and Health Act of 1970 (29 U.S.C. 651 et seq.) as they relate to the protection of the safety and health of workers in the rapidly developing field of biotechnology. Section 8 of the Act authorizes OSHA to inspect workplaces including laboratories and places of employment relating to biotechnology.

FDA 1992 Policy Statement

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 92N-0139]

Statement of Policy: Foods Derived From New Plant Varieties

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a policy statement on foods derived from new plant varieties, including plants developed by recombinant deoxyribonucleic acid (DNA) techniques. This policy statement is a clarification of FDA's interpretation of the Federal Food, Drug, and Cosmetic Act (the act), with respect to new technologies to produce foods, and reflects FDA's current judgment based on new plant varieties now under development in agricultural research. This action is being taken to ensure that relevant scientific, safety, and regulatory issues are resolved prior to the introduction of such products into the marketplace.

DATES: Written comments by August 27, 1992.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Regarding Human Food Issues: James H. Maryanski, Center for Food Safety and Applied Nutrition (HFF-300), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-3617. Regarding Animal Feed Issues: William D. Price, Center for Veterinary Medicine (HFV-221), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8724.

SUPPLEMENTARY INFORMATION:

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I. Background and Overview of Policy

New methods of genetically modifying plants are being used to develop new varieties that will be sources of foods. These methods, including recombinant DNA techniques and cell fusion techniques, enable developers to make genetic modifications in plants, including some modifications that would not be possible with traditional plant breeding methods. This policy discusses the safety and regulatory status of foods derived from new plant varieties, including plants developed by the newer methods of genetic modification.

FDA has received numerous inquiries from industry, government agencies, academia, and the public requesting clarification of the regulatory status of foods, such as fruits, vegetables, grains and their byproducts, derived from new plant varieties developed using recombinant DNA techniques. The questions that FDA has received center on issues such as whether the agency will conduct premarket review of these new foods, whether such foods introduced into interstate commerce would be challenged by FDA on legal grounds, which new plant varieties might come under the jurisdiction of FDA, what scientific information may be necessary to satisfy FDA that such foods are safe and comply with the law, whether petitions would be required by the agency, and whether special labeling would be required.

Representatives of the food biotechnology industry have expressed to FDA the need for strong but appropriate oversight by Federal agencies to ensure public confidence in foods produced by the new techniques. FDA has received several specific comments and suggestions from the industry and from the public concerning Federal oversight of foods developed through new methods of genetically modifying plants (Refs. 1 through 4). The agency has considered these and other documents, including scientific research papers, in developing this notice, and is setting forth this policy statement to clarify its interpretation of the act with respect to human foods and animal feeds [1] derived from new plant varieties, [2] including but not limited to plants developed by new methods of genetic modification.[3]

Under this policy, foods, such as fruits, vegetables, grains, and their byproducts, derived from plant varieties developed by the new methods of genetic modification are regulated within the existing framework of the act, FDA's implementing regulations, and current practice, utilizing an approach identical in principle to that applied to foods developed by traditional plant breeding. The regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective characteristics of the food and the intended use of the food (or its components). The method by which food is produced or developed may in some cases help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product,

[1] "Food" means (1) Articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article (section 201(f) of the act (21 U.S.C. 321(f))). "Food" includes human food, substances migrating to food from food-contact articles, pet food, and animal feed (21 CFR 170.3(m)). "Animal feed" means "an article which is intended for use for food for animals or other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal" (section 201(x) of the act (21 U.S.C. 321(x)).

[2] "Variety" is used here as a general term to describe subgroups (whether varieties or cultivars) of plants within a species developed for desirable traits.

[3] "Genetic modification" means the alteration of the genotype of a plant using any technique, new or traditional. "Modification" is used in a broad context to mean the alteration in the composition of food that results from adding, deleting, or changing hereditary traits, irrespective of the method. Modifications may be minor, such as a single mutation that affects one gene, or major alterations of genetic material that affect many genes. Most, if not all, cultivated food crops have been genetically modified.

rather than the fact that the new methods are used.

The safety of a food is regulated primarily under FDA's postmarket authority of section 402(a)(1) of the act (21 U.S.C. 342(a)(1)). Unintended occurrences of unsafe levels of toxicants in food are regulated under this section. Substances that are expected to become components of food as result of genetic modification of a plant and whose composition is such or has been altered such that the substance is not generally recognized as safe (GRAS) or otherwise exempt are subject to regulation as "food additives" under section 409 of the act (21 U.S.C. 348). Under the act, substances that are food additives may be used in food only in accordance with an authorizing regulation.

In most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to substances commonly found in food, such as proteins, fats and oils, and carbohydrates. As discussed in more detail in section V.C., FDA has determined that such substances should be subject to regulation under section 409 of the act in those cases when the objective characteristics of the substance raise questions of safety sufficient to warrant formal premarket review and approval by FDA. The objective characteristics that will trigger regulation of substances as food additives are described in the guidance section of this notice (section VII.).

The guidance section also describes scientific considerations that are important in evaluating the safety and nutritional value of foods for consumption by humans or animals, regardless of whether the food is regulated under section 402(a)(1) or section 409 of the act. The guidance section outlines a "decision tree" approach to safety assessment of foods derived from new plant varieties that FDA believes is compatible with current practice among scientists knowledgeable in this area. The guidance section also identifies certain scientific questions that may raise sufficient safety concern to warrant consultation with FDA.

Finally, this notice addresses FDA's responsibility under the National Environmental Policy Act (NEPA) and the food labeling provisions of the act as such provisions affect labeling of foods derived from new plant varieties.

This policy statement reflects FDA's current judgment based on the new plant varieties now under development in agricultural research. FDA invites comments on this document. Because scientific developments in this field are occurring rapidly, FDA will refine its policy, if circumstances warrant, in a future **Federal Register** notice. Additionally, FDA plans to announce in a future **Federal Register** notice a workshop to discuss specific scientific issues. FDA invites comment on topics that might be addressed at such a workshop.

II. Responsibility for Food Safety

FDA is the primary Federal agency responsible for ensuring the safety of commerical food and food additives, except meat and poultry products. FDA works closely on food safety matters with the U.S. Department of Agriculture (USDA), which regulates meat and poultry products, and with the U.S. Environmental Protection Agency (EPA), which regulates pesticides and sets tolerances for pesticide residues in food. FDA's authority is under the act, the Public Health Service Act, and FDA's implementing regulations codified in title 21 of the CFR. The act gives FDA broad authority to initiate legal action against a food that is adulterated or misbranded within the meaning of the act.

Producers of new foods have an obligation under the act to ensure that the foods they offer consumers are safe and in compliance with applicable legal requirements. Because in some cases the regulatory jurisdiction of a new food product including those produced using innovative methods may not be clear, producers can informally consult with FDA prior to marketing new foods to ensure that the safety and regulatory status of a new food is properly resolved.

Elsewhere in this issue of the **Federal Register**, FDA announces the filing of the first request by a producer for consultation with FDA concerning a new plant variety developed by recombinant DNA techniques. The request submitted by Calgene, Inc., (Calgene) concerns the FLAVR SAVR™ tomato, a new variety claimed to exhibit improved fruit ripening and other properties. Because Calgene made this request prior to the finalization of this policy statement, FDA advised the firm to submit the information about the tomato initially as a request for advisory opinion under § 10.85 (21 CFR 10.85) to permit the agency to consider the status of the new variety, and to utilize an evaluation process that is open to public comment and permits the agency to make its decision known to the public. Future requests for FDA consultation should be made consistent with the principles outlined in this notice. Thus, FDA does not anticipate that future requests of this nature will be filed under § 10.85

III. Scope of This Document

This notice discusses scientific and regulatory considerations for foods derived from new plant varieties. This notice does not address foods and food ingredients regulated by FDA that have been derived from algae, microorganisms, and other nonplant organisms, including: (1) Foods produced by fermentation, where microorganisms are essential components of the food (e.g., yogurt and single cell protein); (2) food ingredients produced by fermentation, such as many enzymes, flavors, amino acids, sweeteners, thickeners, antioxidants, preservatives, colors, and other substances; (3) substances produced by new plant varieties whose purpose is to color food, and (4) foods derived from animals that are subject to FDA's authority, including seafood. FDA is considering whether to address these issues in future **Federal Register** notices.

Finally, the principles discussed in this notice do not apply to "new drugs" as defined by section 201 (p) of the act (21 U.S.C. 321(p)), "new animal drugs" as defined by section 201(w) of the act (21 U.S.C. 321(w)), or to "pesticide chemicals" as defined by section 201(q) of the act. As discussed in section IX., EPA is responsible for pesticide chemicals, including those produced in plants as a result to genetic modification.

IV. Scientific Issues Relevant to Public Health

Plant breeding is the science of combining desirable genetic traits into a variety that can be used in agriculture. The desired traits can be broadly divided into two classes: Those that affect agronomic characteristics of the plant, and those that affect quality characteristics of the food. Agronomic characteristics include those affecting yield; resistance to diseases, insects, and herbicides; and ability to thrive under various adverse environmental conditions. Quality characteristics include those affecting processing, preservation, nutrition, and flavor.

The genetic modification techniques used to develop new plant varieties constitute a continuum. Traditional breeding typically consists of hybridization between varieties of the same species and screening for progeny with desired characteristics. Such hybridizations only can introduce traits found in close relatives. Breeders have developed or adopted a number of techniques to expand the range of

genetic variation available to them. These techniques introduce variation either by using mutagenesis to alter the genome or by introducing or modifying DNA segments, including DNA segments derived from other organisms.

Mutagenic techniques include both random mutagenesis, resulting from treatment with chemical and physical mutagens, and somaclonal variation, whereby, with the use of tissue culture techniques, plants are regenerated from callus or leaf tissue explants. The regenerated plants often have properties not found in the progenitor plant, reflecting both preexisting cellular genetic differences and tissue-culture induced mutations. The mutations range from single gene changes to chromosomal rearrangements. Mutagenesis techniques are limited, however, by their inability to target a desired trait. Somaclonal variants also frequently are unstable or infertile.

Techniques for gene transfer between plants that belong to different species or genera fall under the general heading of "wide crosses." These "crosses" have been accomplished using hybridization, and protoplast fusion. Traditional wide crosses involve hybridization between closely related species or genera, frequently requiring the use of special techniques such as embryo rescue and chromosome doubling to overcome physical or genetic barriers to the production of fertile progeny. They permit the transfer of genetic traits that are not present in close relatives of the modern plant varieties but are found in more distant wild relatives. Traits that confer resistance to a number of diseases have been introduced this way.

All of the techniques described above require extensive back crossing with the parent line [4] to eliminate mutations unlinked to that responsible for the desired phenotype and undesirable traits in extraneous genetic material introduced along with that encoding the desired trait.

Recombinant DNA techniques involve the isolation and subsequent introduction of discrete DNA segments containing the gene(s) of interest into recipient (host) plants. The DNA segments can come from any organism (microbial, animal, or plant). In theory, essentially any trait whose gene has been identified can be introduced into virtually any plant, and can be introduced without extraneous unwanted genetic material. Since these techniques are more precise, they increase the potential for safe, better-characterized, and more predictable foods.

DNA segments introduced using the new techniques insert semi-randomly into the chromosome, frequently in tandem multiple copies, and sometimes in more than one site on the chromosome. Both the number of copies of the gene and its location in the chromosome can affect its level of expression, as well as the expression of other genes in the plant. To ensure homozygosity and to enhance the stability of the line and the ability to cross the trait into other lines, the breeder will often perform a limited number of back crosses to ensure that the plant line has the new trait inserted in only one location in the chromosome.

Additionally, as with other breeding techniques, the phenotypic effects of a new trait may not always be completely predictable in the new genetic background of the host. Therefore, it is common practice for breeders using recombinant DNA techniques to cross the new trait into a number of hosts to find the best genetic background for expression of the new trait. Currently, for most crops only a few lines or varieties of any species are amendable to the use of recombinant DNA techniques. Once the desired trait is introduced into a line amenable to the technique, it must then be crossed by traditional means to other desired lines or varieties.

Regardless of the particular combination of techniques used, the development of a new plant variety typically will require many site-years (number of sites x number of years of plant testing) of performance trials before introduction into agricultural practice. These range from as few as 10 to 20 site-years for some plants to 75 to 100 site-years for others (some 5 to 10 years). The time of evaluation and the size and number of sites will vary as necessary to confirm performance; to reveal vulnerabilities to pests, diseases, or other production hazards; to evaluate stability of the phenotype; to evaluate characteristics of the food; to evaluate environmental effects; and to produce the required amount of seed before the new plant variety can be grown commercially by farmers. In the course of this intensive assessment, individual plants exhibiting undesirable traits are eliminated.

Recombinant DNA techniques are used to achieve the same types of goals as traditional techniques: The development of new plant varieties with enhanced agronomic and quality characteristics. Currently, over 30 different agricultural crops developed using recombinant DNA techniques are in field trials. Food crops have been developed using these techniques to exhibit improved resistance to pests and disease and to chemical herbicides. For example, a plant's ability to resist insect infestation reportedly has been improved by transferring bacterial genetic material that encodes proteins toxic to certain insects (e.g., *Bacillus thuringiensis delta* endotoxin). Other plants have been given viral coat-protein genes that confer cross-protection to viral pathogens.

Other new plant varieties have been developed that exhibit traits for improved food processing, improved nutritional content, or enhanced protection against adverse weather conditions. For example, genetic modifications of plant enzymes involved in fruit ripening may yield tomatoes with improved ripening characteristics, texture, and flavor. Scientists have used recombinant DNA techniques to transfer genetic material for the production of seed storage protein conferring improvements in nutritional balance of important amino acids in the new plant varieties. Scientists have also identified genes in certain fish that encode proteins that conferee increased resistance to cold. Copies of these genes have been introduced into agricultural crops with the goal of producing new plant varieties that show improved tolerance to cold weather conditions.

These examples illustrate only a few of the many improved agronomic and food processing traits currently being introduced into plants using recombinant DNA techniques. Any genetic modification technique has the potential to alter the composition of food in a manner relevant to food safety, although, based on experience, the likelihood of a safety hazard is typically very low. The following paragraphs describe some potential changes in composition that may require evaluation to assure food safety.

A. Unexpected Effects

Virtually all breeding techniques have potential to create unexpected (including pleiotropic [5] effects. For example, mutations unrelated to the desired modification may be induced; undesirable traits may be introduced along with the desired traits; newly introduced DNA may physically insert into a transcriptionally active site on the chromosome, and may thereby inactivate a host gene or alter control of

[4] A line is a group of individuals from a common ancestry. It is a more narrowly defined group than a variety. (Breeding Field Crops, J.M. Poehlman, Van Nostrand Reinhold, New York, 1987.

[5] Pleiotropic effects refer to multiple effects resulting from a single genetic change.

its expression; the introduced gene product or a metabolic product affected by the genetic change may interact with other cellular products to produce a deleterious effect. Plant breeders using well established practices have successfully identified and eliminated plants that exhibit unexpected, adverse traits prior to commercial use.

B. Known Toxicants

Plants are known to produce naturally a number of toxicants and antinutritional factors, such as protease inhibitors, hemolytic agents, and neurotoxins, which often serve the plant as natural defense compounds against pests or pathogens. For example, most cereals contain protease inhibitors, which can diminish the nutritive value of proteins. Many legumes contain relatively high levels of lectins and cyanogenic glycosides. Lectins, if not destroyed by cooking or removed by soaking, can cause severe nausea, vomiting, and diarrhea. Cyanogenic glycosides can be hydrolyzed by specific enzymes in the plant to release cyanide if food from the plant is improperly prepared. The levels of cyanogenic glycosides in cassava and some legumes can lead to death or chronic neurological disease if these foods are eaten uncooked. Cruciferae contain glucosinolates which may impair thyroid function. Squash and cucumber contain cucurbiticin, an acute toxicant. Chickpeas contain lathyrogens, which are neurotoxins.

Many of these toxicants are present in today's foods at levels that do not cause acuate toxicity. Others, such as in cassava and some legumes, are high enough to cause severe illness or death if the foods are not properly prepared. FDA seek to assure that new plant varieties do not have significantly higher levels of toxicants than present in other edible varieties of the same species.

Plants, like other organisms, have metabolic pathways that no longer function due to mutations that occurred during evolution. Products or intermediates of some such pathways may include toxicants. In rare cases, such silent pathways may be activated by mutations, chromosomal rearrangements, or new regulatory regions introduced during breeding, and toxicants hitherto not associated with a plant species may thereby be produced. Similarly, toxicants ordinarily produced at low levels in a plant may be produced at high levels in a new variety as a result of such occurrences. The likelihood of activation of quiescent pathways or increased expression from active pathways is considered extremely low in food plants with a long history of use that have never exhibited production of unknown or unexpected toxins, since the genetic changes that can lead to such events occur during growth and are induced with traditional breeding manipulations. In the few cases where toxicants have been raised to unsafe levels in a commercial plant variety, the toxicants were known to occur in significant levels in one of the parent species. Except in rare cases, plant breeders using well established practices have successfully identified and eliminated plants that express unacceptably high levels of toxicants prior to commercial use.

C. Nutrients

Another unintended consequence of genetic modification of the plant may be a significant alteration in levels of important nutrients. In addition, changes in bioavailability of a nutrient due to changes in form of the nutrient or the presence of increased levels of other constituents that affect absorption or metabolism of nutrients must be considered for potential nutritional impact.

D. New Substances

Because plant breeders using the new techniques are able to introduce essentially any trait or substance whose molecular genetic identity is known into virtually any plant, it is possible to introduce a protein that differs significantly in structure or function, or to modify a carbohydrate, fat or oil, such that it differs significantly in composition from such substances currently found in food.

E. Allergenicity

All food allergens are proteins. However, only a small fraction of the thousands of proteins in the diet have been found to be food allergens. FDA's principal concern regarding allergencity is that proteins transferred from one food source to another, as is possible with recombinant DNA and protoplast fusion techniques, might confer on food from the host plant the allergenic properties of food from the donor plant. Thus, for example, the introduction of a gene that encodes a peanut allergen into corn might make that variety of corn newly allergenic to people ordinarily allergic to peanuts.

Examples of foods that commonly cause an allergenic response are milk, eggs, fish, crustacea, molluscs, tree nuts, wheat, and legumes (particularly peanuts and soybeans). The sensitive population is ordinarily able to identify and avoid the offending food. However, if the allergen were moved into a variety of a plant species that never before produced that allergen, the susceptible population would not know to avoid food from that variety.

In some foods that commonly cause an allergic response, the particular protein(s) responsible for allergenicity is known, and therefore the producer may know whether the transferred protein is the allergen. However, in other cases, the protein responsible for a food's allergenicity is not known, and FDA considers it prudent practice for the producer initially to assume that the transferred protein is the allergen. Appropriate in vitro or in vivo allergenicity testing may reveal whether food from the new variety elicits an allergenic response in the potentially sensitive population (i.e., people sensitive to the food in which the protein is ordinarily found). Producers of such foods should discuss allergenicity testing protocol requirements with the agency. Labeling of foods newly containing a known or suspect allergen may be needed to inform consumers of such potential.

A separate issue is whether any new protein in food has the potential to be allergenic to a segment of the population. At this time, FDA is unaware of any practical method of predict or assess the potential for new proteins in food to induce allergenicity and requests comments on this issue.

F. Antibiotic Resistance Selectable Markers

In gene transfer experiments, only a small percentage of the recipient plant cells will actually take up the introduced genes, and many desirable traits (i.e., those that specify the intended technical effect) are not easy to detect before the plant has fully developed. Scientists, therefore, enhance their ability to isolate plant cells that have taken up and stably incorporated the desired genes by physically linking the desired gene to a selectable marker gene, such as a gene that specifies the production of a substance that inactivates antibiotics.

The kanamycin resistance gene is one of the most widely used selectable marker genes. The kanamycin resistance gene specifies the information for the production of the enzyme, aminoglycoside 3'-phosphotransferase II. The common name for this enzyme is kanamycin (or neomycin) phosphotransferase II. The kanamycin phosphotransferase II enzyme modifies aminoglycoside antibiotics, including kanamycin, neomycin, and geneticin (G418), chemically inactivating the antibiotic and rendering the cells that produce the kanamycin resistance gene product refractory or resistant to the

antibiotic. Plant cells that have received and stably express the kanamycin resistance gene survive and replicate on laboratory media in the presence of the antibiotic, kanamycin. Plant cells that did not take up and express the introduced kanamycin resistance gene will be killed by the antibiotic. By linking the selectable marker gene to another gene that specifies a desired trait, scientists can identify and select plants that have taken up and express the desired genes.

The kanamycin resistance gene has been used as a selectable marker in more than 30 crops to develop varieties that exhibit improved nutritional and processing properties, resistance to pests and diseases, tolerance to chemical herbicides, and other agronomic properties. Once the desired plant variety has been selected, the kanamycin resistance gene serves no further useful purpose, although it continues to produce the kanamycin phosphotransferase II enzyme in the plant tissues. Thus, while the kanamycin resistance gene is a research tool that is important for developing new plant varieties through the current recombinant DNA techniques of gene transfer, both the kanamycin resistance gene and its product, the kanamycin phosphotransferase II enzyme protein, are expected to be present in foods derived from such plants, unless removed through recently developed techniques (Ref. 5).

Selectable marker genes that produce enzymes that inactivate clinically useful antibiotics theoretically may reduce the therapeutic efficacy of the antibiotic when taken orally if the enzyme in the food inactives the antibiotic. FDA believes that it will be important to evaluate such concerns with respect to commercial use of antibiotic resistance marker genes in food, especially those that will be widely used. FDA is now evaluating this and other issues with respect to the use of the kanamycin resistance marker in food. (See 56 FR 20004, May 1, 1991.)

G. Plants Developed to Make Specialty Nonfood Substances

New genetic modification techniques may develop plants that produce nonfood chemicals, such as polymers and pharmaceuticals. In many cases, the plant will not subsequently be used for food. In such cases, the developer must ensure that food-use varieties of the crop do not cross with or become mixed with the nonfood-use varieties. This is not a new issue for breeders and growers. For example, some varieties of rapeseed oil are grown for industrial oil use, and have high levels of toxicants, such as erucic acid and glucosinylates, while other varieties are grown for food use and have low levels of these substances. Similarly, potatoes grown for industrial uses can have higher levels of solanine than those grown for retail food use. The producer of the oil or potato must ensure that the edible plant variety is not adulterated within the meaning of the act. Developers of crops designed to produce specialty nonfood substances have a comparable obligation.

If plants (or materials derived from plants) used to make nonfood chemicals are also intended to be used for food, producers should consult with FDA to determine whether the nonfood chemical would be a food additive requiring an authorizing regulation prior to marketing for food use.

H. Issues Specific to Animal Feeds

Unlike a food in the human diet, an animal feed derived from a single plant may constitute a significant portion of the animal diet. For instance, 50 to 75 percent of the diet of most domestic animals consists of field corn. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet.

Further, animals consume plants, plant parts, and plant byproducts that are not consumed by humans. For example, animals consume whole cottonseed meal, whereas humans consume only cotton seed oil. Gossypol, a plant toxicant, is concentrated in the cotton seed meal during the production of cotton seed oil. Because plant byproducts represent an important feed source for animals, it is important to determine if significant concentrations of toxicants or other harmful plant constituents are present in new plant varieties.

Nutrient composition and availability of nutrients in feed are important safety considerations for animal health. For example, if a genetic modification in soybeans caused an increase in phytin content, the soybean feed may need to be supplemented with phosphorous to avoid problems of animal health.

V. Regulatory Status of Foods Derived From New Plant Varieties

A. The Statutory Framework for New Foods and Food Ingredients

The United States today has a food supply that is as safe as any in the world. Most foods derived from plants predate the establishment of national food laws, and the safety of these foods has been accepted based on extensive use and experience over many years (or even centuries). Foods derived from new plant varieties are not routinely subjected to scientific tests for safety, although there are exceptions. For example, potatoes are generally tested for the glycoalkaloid, solanine. The established practices that plant breeders employ in selecting and developing new varieties of plants, such as chemical analyses, taste testing, and visual analyses, rely primarily on observations of quality, wholesomeness, and agronomic characteristics. Historically, these practices have proven to be reliable for ensuring food safety. The knowledge from this past experience coupled with safe practices in plant breeding has contributed to continuous improvements in the quality, variety, nutritional value, and safety of foods derived from plants modified by a range of traditional and increasingly sophisticated techniques (Ref. 1 at xvi). Based on this record of safe development of new varieties of plants, FDA has not found it necessary to conduct, prior to marketing, routine safety reviews of whole foods derived from plants.

Nevertheless, FDA has ample authority under the act's food safety provisions to regulate and ensure the safety of foods derived from new plant varieties, including plants developed by new techniques. This includes authority to require, where necessary, a premarket safety review by FDA prior to marketing of the food. Under section 402(a)(1) of the act, a food is deemed adulterated and thus unlawful if it bears or contains an added poisonous or deleterious substance that may render the food injurious to health or a naturally occurring substance that is ordinarily injurious. Section 402(a)(1) of the act imposes a legal duty on those who introduce food into the market place, including food derived from new crop varieties, to ensure that the food satisfies the applicable safety standard. Foods that are adulterated under section 402(a)(1) of the act are subject to the full range of enforcement measures under the act, including seizure, injunction, and criminal prosecution of those who fail to meet their statutory duty.

FDA has relied almost exclusively on section 402(a)(1) of the act to ensure the safety of whole foods. Toxins that occur naturally in food and that render the food ordinarily injurious to health (such as poisons in certain mushrooms), and thus adulterated, rarely required FDA regulatory action because such cases are typically well known and carefully avoided by food producers.

FDA regards any substance that is not an inherent constituent of food or whose level in food has been increased by human intervention to be "added" within the meaning of section 402(a)(1) of the act. See *United States* v. *Anderson Seafoods, Inc.*, 622 F. 2d 157 (5th Cir. 1980). Added substances are subject to the more stringent "may render [the food] injurious" safety standard. Under this standard, the food is adulterated if, by virtue of the presence of the added substance, there is a "reasonable possibility" that consumption of the food will be injurious to health. *United States* v. *Lexington Mill & Elevator Co.*, 232 U.S. 399 (1914). The "may render injurious" standard would apply to a naturally occurring toxin in food if the level of the toxin in a new plant variety were increased through traditional plant breeding or some other human intervention. Section 402(a)(1) of the act would have been the legal basis under which FDA could have blocked marketing in the 1970's of a new variety of potato that had been found during its development to contain elevated and potentially harmful levels of solanine as a result of a cross with an inedible wild potato.

Section 402(a)(1) of the act is most frequently used by FDA to regulate the presence in food of unavoidable environmental contaminants such as lead, mercury, dioxin, and aflatoxin. FDA regulary establishes action levels and takes enforcement action to prevent the sale of foods that contain unacceptable levels of such unintended and undesired contaminants.

Section 402(a)(1) of the act was signed into law in 1938 and has its origins in a similar provision in the Federal Food and Drugs Act of 1906. Until 1958, this authority was the principal tool relied upon by FDA to regulate the safety of food and food ingredients. In 1958, in response to public concern about the increased use of chemicals in foods and food processing and with the support of the food industry, Congress enacted the Food Additives Amendment (the amendment) to the act. Among other provisions, the amendment established a premarket approval requirement for "food additives." The basic thrust of the amendment was to require that, before a new chemical additive (such as a preservative, antioxidant, emulsifier, or artificial flavor) could be used in food processing, its producer must demonstrate the safety of the additive to FDA. Congress recognized under this new scheme that the safety of an additive could not be established with absolute certainty or under all conditions of use. Congress thus provided for a science-based safety standard that requires producers of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of the additive. See 21 CFR 170.3(i). If FDA finds an additive to be safe, based ordinarily on data submitted by the producer to the agency in a food additive petition, the agency promulgates a regulation specifying the conditions under which the additive may be safely used. Food additives that are not the subject of such a regulation are deemed unsafe as a matter of law, and the foods containing them are adulterated under section 402(a)(2)(C) of the act (21 U.S.C. 342(a)(2)(C)) and are thus unlawful.

In enacting the amendment, Congress recognized that many substances intentionally added to food do not require a formal premarket review by FDA to assure their safety, either because their safety had been established by a long history of use in food or because the nature of the substance and the information generally available to scientists about the substance are such that the substance simply does not raise a safety concern worthy of premarket review by FDA. Congress thus adopted a two-step definition of "food additive." The first step broadly includes any substance the intended use of which results in its becoming a component of food. The second step, however, excludes from the definition of food additive substances that are GRAS. It is on the basis of the GRAS exception of the "food additive" definition that many ingredients derived from natural sources (such as salt, pepper, vinegar, vegetable oil, and thousands of spices and natural flavors), as well as a host of chemical additives (including some sweeteners, preservatives, and artificial flavors), are able to be lawfully marketed today without having been formally reviewed by FDA and without being the subject of a food additive regulation. The judgment of Congress was that subjecting every intentional additive to FDA premarket review was not necessary to protect public health and would impose an insurmountable burden on FDA and the food industry.

Congress' approach to defining food additives means, however, that companies developing new ingredients, new versions of established ingredients, or new processes for producing a food or food ingredient must make a judgment about whether the resulting food substance is a food additive requiring premarket approval by FDA. In many cases, the answer is obvious, such as when the ingredient is a man made chemical having no widely recognized history of safe use in food. Such an ingredient must be approved prior to its use by the issuance of a food additive regulation, based on information submitted to FDA in a food additive petition.

In other cases, the answer is less obvious, such as when an established ingredient derived from nature is modified in some minor way or produced by a new process. In such cases, the manufacturer must determine whether the resulting ingredient still falls within the scope of any existing food additive regulation applicable to the original ingredient or whether the ingredient is exempt from regulation as a food additive because it is GRAS. The GRAS status of some substances is recognized in FDA's regulations (21 CFR parts 182, 184, 186, 582, and 584), but FDA has not attempted to include all GRAS substances in its regulations.

FDA has traditionally encouraged producers of new food ingredients to consult with FDA when there is a question about an ingredient's regulatory status, and firms routinely do so, even though such consultation is not legally required. If the producer begins to market the ingredient based on the producer's independent determination that the substance is GRAS and FDA subsequently concludes the substance is not GRAS, the agency can and will take enforcement action to stop distribution of the ingredient and foods containing it on the ground that such foods are or contain an unlawful food additive.

FDA considers the existing statutory authority under sections 402(a)(1) and 409 of the act, and the practical regulatory regime that flows from it, to be fully adequate to ensure the safety of new food ingredients and foods derived from new varieties of plants, regardless of the process by which such foods and ingredients are produced. The existing tools provide this assurance because they impose a clear legal duty on producers to assure the safety of foods they offer to consumers; this legal duty is backed up by strong enforcement powers; and FDA has authority to require premarket review and approval in cases where such review is required to protect public health.

In the Federal Register of June 26, 1986 (51 FR 23302) (the June 1986 notice), FDA, in conjunction with the Office of Science and Technology Policy in the Executive Office of the President, described FDA's current food safety authorities and stated the agency's intention to regulate foods produced by

new methods, such as recombinant DNA techniques, within the existing statutory and regulatory framework. This notice reaffirms that intention. The following paragraphs explain briefly how the current framework will apply specifically to foods derived from new plant varieties, including plants developed by recombinant DNA techniques.

B. The Application of Section 402(a)(1) of the Act

Section 402(a)(1) of the act will continue to be FDA's primary legal tool for regulating the safety of whole foods, including foods derived from plants genetically modified by the new techniques. Section 402(a)(1) of the act will be applied to any substance that occurs unexpectedly in the food at a level that may be injurious to health. This includes a naturally occurring toxicant whose level is unintentionally increased by the genetic modification, as well as an unexpected toxicant that first appears in the food as a result of pleiotropic effects. Such substances are regarded by FDA as added substances whose presence adulterates the food if present at a level that "may render" the food injurious to health.

It is the responsibility of the producer of a new food to evaluate the safety of the food and assure that the safety requirement of section 402(a)(1) of the act is met. In section VII., FDA provides guidance to the industry regarding prudent, scientific approaches to evaluating the safety of foods derived from new plant varieties, including the safety of the added substances that are subject to section 402(a)(1) of the act. FDA encourages informal consultation between producers and FDA scientists to ensure that safety concerns are resolved. However, producers remain legally responsible for satisfying section 402(a)(1) of the act, and they will continue to be held accountable by FDA through application of the agency's enforcement powers.

C. The Application of Section 409 of the Act

When Congress enacted the amendment in 1958, it did not explicitly address the possible application of the food additive approval process to foods derived from new plant varieties. As previously discussed, such foods have historically been regulated successfully under section 402(a)(1) of the act. The new methods of genetic modification have focused attention, however, on the possibility that intended changes in the composition of food resulting from genetic modification might be of a nature sufficient as a legal and public health matter to trigger regulation of a component of the food under section 409 of the act.

As discussed above, the food additive definition broadly encompasses any substance that has an intended use in food, unless the substance is GRAS. It was on this basis that the June 1986 notice indicated that, in some cases, whole foods derived from new plant varieties, including plants developed by new genetic modification techniques, might fall within the scope of FDA's food additive authority. Indeed, FDA's regulations have long recognized that it might be appropriate in some circumstances to review the GRAS (and implicitly food additive) status of foods or substances of natural biological origin that have a history of safe use but which subsequently have had "significant alteration by breeding and selection." (See 21 CFR 170.30(f).) As already discussed, however, FDA has rarely had occasion to review the GRAS status of foods derived from new plant varieties because these foods have been widely recognized and accepted as safe.

FDA has reviewed its position on the applicability of the food additive definition and section 409 of the act to foods derived from new plant varieties in light of the intended changes in the composition of foods that might result from the newer techniques of genetic modification. The statutory definition of "food additive" makes clear that it is the intended or expected introduction of a substance into food that makes the substance potentially subject to food additive regulation. Thus, in the case of foods derived from new plant varieties, it is the transferred genetic material and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS.

In regulating foods and their byproducts derived from new plant varieties, FDA intends to use its food additive authority to the extent necessary to protect public health. Specifically, consistent with the statutory definition of "food additive" and the overall design of FDA's current food safety regulatory program, FDA will use section 409 of the act to require food additive petitions in cases where safety questions exist sufficient to warrant formal premarket review by FDA to ensure public health protection.

With respect to transferred genetic material (nucleic acids), generally FDA does not anticipate that transferred genetic material would itself be subject to food additive regulation. Nucleic acids are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food. In regulatory terms, such material is presumed to be GRAS. Although the guidance provided in section VII. calls for a good understanding of the identity of the genetic material being transferred through genetic modification techniques, FDA does not expect that there will be any serious question about the GRAS status of transferred genetic material.

FDA expects that the intended expression product or products present in foods derived from new plant varieties will typically be proteins or substances produced by the action of protein enzymes, such as carbohydrates, and fats and oils. When the substance present in the food is one that is already present at generally comparable or greater levels in currently consumed foods, there is unlikely to be a safety question sufficient to call into question the presumed GRAS status of such naturally occurring substances and thus warrant formal premarket review and approval by FDA. Likewise, minor variations in molecular structure that do not affect safety would not ordinarily affect the GRAS status of the substances and, thus, would not ordinarily require regulation of the substance as a food additive.

It is possible, however, that the intended expression product in a food could be a protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food. Such substances may not be GRAS and may require regulation as a food additive. For example, if a food derived from a new plant variety contains a novel protein sweetener as a result of the genetic modification of the plant, that sweetener would likely require submission of a food additive petition and approval by FDA prior to marketing. FDA invites comments on substances, in addition to proteins, carbohydrates, and fats and oils, that in the future may be introduced into foods by genetic modification.

Section VII. of this notice provides guidance to producers of new foods for conducting safety evaluations. This guidance is intended to assist producers in evaluating the safety of the food that they market, regardless of whether the food requires premarket approval by FDA. This guidance also includes criteria and analytical steps that producers can follow in determining whether their product is a candidate for food additive regulation and whether consultation with FDA should be pursued to determine the regulatory

status of the product. Ultimately, it is the food producer who is responsible for assuring safety.

FDA has long regarded it to be a prudent practice for producers of foods using new technologies to work cooperatively with the agency to ensure that the new products are safe and comply with applicable legal requirements. It has been the general practice of the food industry to seek informal consultation and cooperation, and this practice should continue with respect to foods produced using the newer techniques of genetic modification.

VI. Labeling

FDA has received several inquiries concerning labeling requirements for foods derived from new plant varieties developed by recombinant DNA techniques. Section 403(i) of the act (21 U.S.C. 343(i)) requires that a producer of a food product describe the product by its common or usual name or in the absence thereof, an appropriately descriptive term (21 U.S.C. part 101.3) and reveal all facts that are material in light of representations made or suggested by labeling or with respect to consequences which may result from use (21 U.S.C. 343(a); 21 U.S.C. 321(n)). Thus, consumers must be informed, by appropriate labeling, if a food derived from a new plant variety differs from its traditional counterpart such that the common or usual name no longer applies to the new food, or if a safety or usage issue exists to which consumers must be alerted.

For example, if a tomato has had a peanut protein introduced into it and there is insufficient information to demonstrate that the introduced protein could not cause an allergic reaction in a susceptible population, a label declaration would be required to alert consumers who are allergic to peanuts so they could avoid that tomato, even if its basic taste and texture remained unchanged. Such information would be a material fact whose omission may make the label of the tomato misleading under section 403(a) of the act (21 U.S.C. 343(a)).

FDA has also been asked whether foods developed using techniques such as recombinant DNA techniques would be required to bear special labeling to reveal that fact to consumers. To date, FDA has not considered the methods used in the development of a new plant variety (such as hybridization, chemical or radiation-induced mutagenesis, protoplast fusion, embryo rescue, somaclonal variation, or any other method) to be material information within the meaning of section 201(n) of the act (21 U.S.C. 321(n)). As discussed above, FDA believes that the new techniques are extensions at the molecular level of traditional methods and will be used to achieve the same goals as pursued with traditional plant breeding. The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding. For this reason, the agency does not believe that the method of development of a new plant variety (including the use of new techniques including recombinant DNA techniques) is normally material information within the meaning of 21 U.S.C. 321(n) and would not usually be required to be disclosed in labeling for the food.

The guidance section (section VII.) of this notice discusses certain circumstances where questions may arise about the proper labeling of foods derived from new plant varieties. FDA requests comments on the labeling of foods derived from new plant varieties, including plants developed with recombinant DNA techniques.

VII. Guidance to Industry for Foods Derived From New Plant Varieties

A. Introduction

This guidance section describes many of the scientific considerations for evaluating the safety and nutritional aspects of food from new plant varieties derived by traditional methods (such as hybridization or mutagenesis), tissue culture methods (such as somaclonal variation and protoplast fusion), and recombinant DNA methods. Although some of the safety considerations are specific to individual technologies, many safety considerations are similar regardless of the technology used. This guidance section does not attempt to delineate acceptable practices for each specific technology. FDA expects plant breeders to adhere to currently accepted scientific standards of practice within each technology. This guidance section is based on existing practices followed by the traditional plant breeders to assess the safety and nutritional value of new plant varieties and is not intended to alter these long-established practices, or to create new regulatory obligations for them.

This guidance section describes food safety and nutritional concerns, rather than performance characteristics for which the new plant varieties may have been developed. However, this guidance section cannot identify all safety and nutritional questions that could arise in a given situation and, while comprehensive, should not be viewed as exhaustive. In some cases, additional factors may need to be considered, while in other situations, some of the factors may not apply. Therefore, this guidance section also describes situations in which producers should consult with FDA on scientific issues, the design of appropriate test protocols, requirements for labeling, and whether a food additive petition may be required.

Genetic modifications of plants can have unintended or unexpected effects on the phenotype of the plant, such as poor growth or reduced tolerance to conditions of environmental stress, that are readily apparent and can be effectively managed by appropriate selection procedures. However, effects such as an alteration in the concentration of important nutrients, increases in the level of natural toxicants, or the transfer of allergens from one species to another may not be readily detected without specific test procedures. FDA believes that a scientific basis should exist to establish that new plant varieties do not exhibit unacceptable effects with respect to toxicants, nutritional value, or allergens. In cases where the host plant has little or no history of safe use, the assessment of new plant varieties should include evidence that unknown toxicants are not present in the new plant variety at levels that would be injurious to health.

In addition, by using recombinant DNA techniques, plant breeders are now capable theoretically of introducing essentially any trait (and thus substance) whose molecular genetic identity is known into virtually any plant due to the increased power and precision of recombinant DNA techniques. This guidance section, however, discusses only proteins, carbohydrates, and fats and oils, in the belief that these are the principal substances that are currently being intentionally modified or introduced into new plant varieties. Using the new techniques, it is possible to introduce a gene that encodes a protein that differs significantly in structure or function, or to modify a carbohydrate, or fat or oil, such that it differs significantly in composition from such substances currently found in food. FDA believes that plant breeders must carefully evaluate the potential for adverse effects that could result from the presence of these substances in new plant varieties.

Theoretically, genetic modifications have the potential to activate cryptic

pathways synthesizing unknown or unexpected toxicants, or to increase expression from active pathways that ordinarily produce low or undetectable levels of toxicants. However, this potential has been effectively managed in the past by sound agricultural practices. The agency believes that the use of host plants with a history of safe use, coupled with a continuation of sound agricultural practice, will minimize the potential for adverse public health consequences that may arise from increased levels of unknown or unexpected toxicants.

This guidance section provides a basis for determining whether new plant varieties are as safe and nutritious as their parental varieties. The assessment scheme focuses on characteristics of the new plant variety, based on characteristics of the host and donor species, the nature of the genetic change, the identity and function of newly introduced substances, and unexpected or unintended effects that accompany the genetic change. The assessment focuses on the following considerations:

1. Toxicants known to be characteristic of the host and donor species;

2. The potential that food allergens will be transferred from one food source to another;

3. The concentration and bioavailability of important nutrients for which a food crop is ordinarily consumed;

4. The safety and nutritional value of newly introduced proteins; and

5. The identity, composition and nutritional value of modified carbohydrates, or fats and oils.

The scientific concepts described in this guidance section are consistent with the concepts of substantial equivalence of new foods discussed in a document under development by the Group of National Experts on Safety in Biotechnology of the Organization for Economic Cooperation and Development (OECD). This guidance section is also consistent with the principles for food safety assessment discussed in the Report of a Joint Food and Agriculture Organization/World Health Organization Consultation (Ref. 6).

B. Flow Charts

The flow charts presented in sections VII.D. through VII.F. (Figures 2 through 6) outline a series of questions related to the safety and nutritional value of foods derived from the new plant variety, and are intended to provide general guidance to breeders and developers. FDA intends that these flow charts be used in conjunction with other information and practices that breeders and developers rely on to develop new plant varieties. These reflect the current state of scientific information and are not intended as regulatory requirements. As new information is developed, FDA anticipates that the flow charts may require modification.

The summary flow chart (Figure 1) presented in this section is a synopsis of FDA's safety assessment process. It describes, in a general way, the assessment for unexpected or unintended effects that may arise as a result of the specific characteristics that are associated with the host plant and donor(s), as well as the assessment of the expected or intended effects. Because Figure 1 is a summary, it should not be relied upon for a safety assessment. The boxes labeled Figure 2, Figure 3, Figure 4, and Figures 5 and 6, respectively, refer to more specific flow charts that describe, in appropriate detail, the safety assessment from the perspective of the host, donor, and new substances that are introduced into the new plant variety.

Sections VII.D. through VII.F. address the scientific considerations pertaining to the host plant, donor(s), and new substances in more detail. Each section describes information that relates to the safety assessment, presents a flow chart that summarizes the safety assessment, discusses each of the questions in that flow chart, and describes the endpoints that are reached in that flow chart.

There are three endpoints in the flow charts in this notice: (1) No concerns, (2) new variety not acceptable, and (3) consult FDA. The notes to each individual flow chart discuss the interpretation of these endpoints in relation to that particular flow chart. In general, the interpretation of "no concerns" or "new variety not acceptable" is similar for each flow chart. The endpoint "consult FDA" means that producers may need to consult FDA on regulatory questions, such as whether a food additive petition or special labeling is needed, or on technical questions, such as appropriate testing protocols or specific scientific issues.

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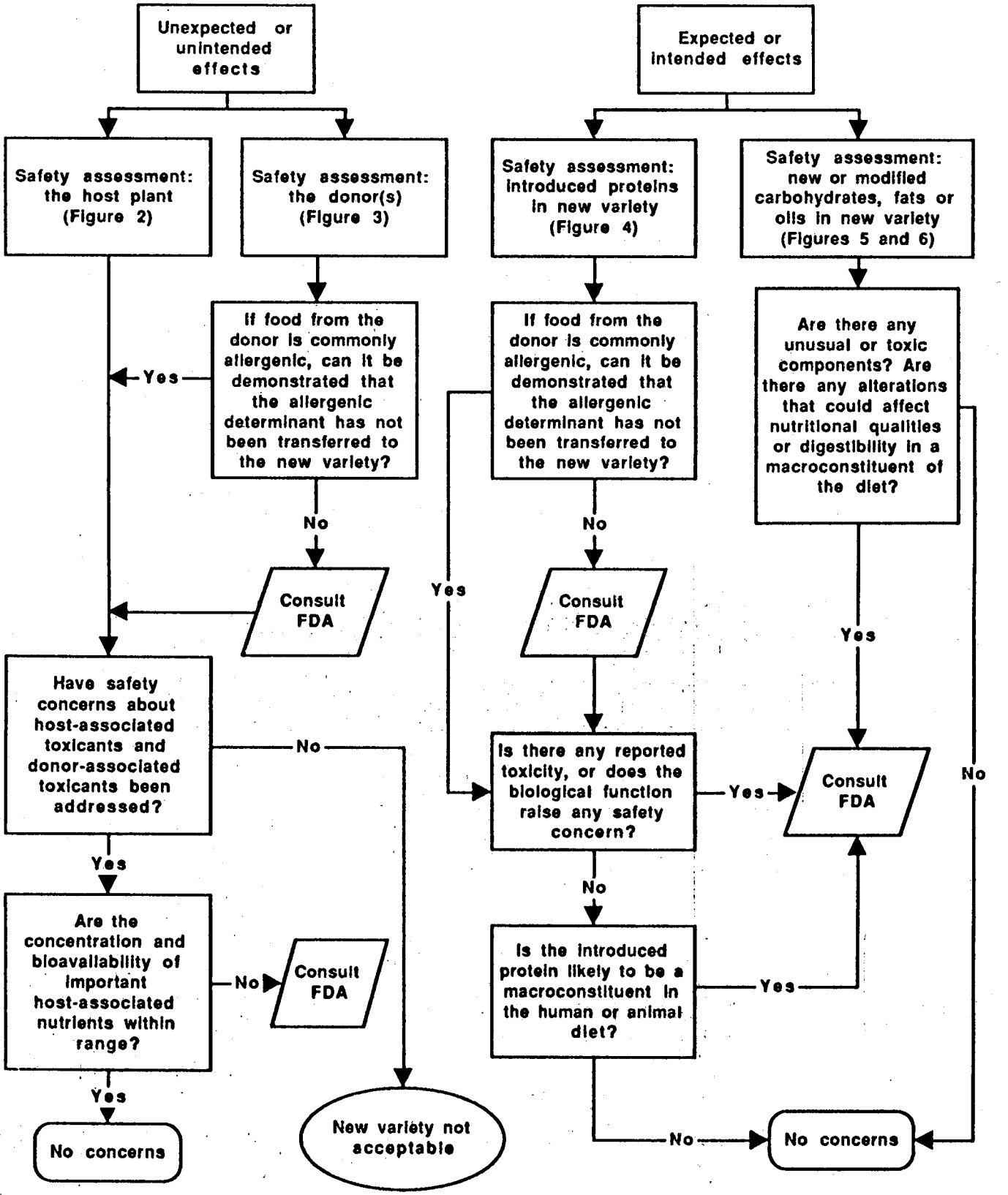

Figure 1. Safety Assessment of New Varieties: Summary

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C. Effects of Processing

Processing (e.g., cooking) may affect the safety of a substance. This is particularly important in the safety assessment of proteins transferred from one food source to another. For example, lectins, which are inactivated by cooking, would raise a safety concern if transferred from kidney beans, which are eaten cooked, to tomatoes, which may be eaten raw. The effects of any potential differences in food processing between the donor and the new plant variety should be carefully considered at each stage in the safety assessment.

D. The Host Plant

A premise basic to this guidance section is that a long history of safe use of the host species in food provides much information regarding the potential of new plant varieties to produce toxicants and antinutrients (substances that adversely affect the nutritional quality of food). In assessing the potential of the host plant to contribute unexpected harmful substances, producers should consider attributes of the host plant and its progenitors such as the following:

1. Taxonomy.

a. Variety name.

b. Known phenotypes and relevant genotypes.

2. Other species or varieties that have previously contributed genetic information to the host.

3. History of safe use.

a. Extent of previous experience.

b. The part of the plant used as food.

c. The presence and identity of potentially harmful constituents such as toxicants and antinutrients.

d. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.

4. The identity and level of nutrients for which the food is consumed.

Figure 2

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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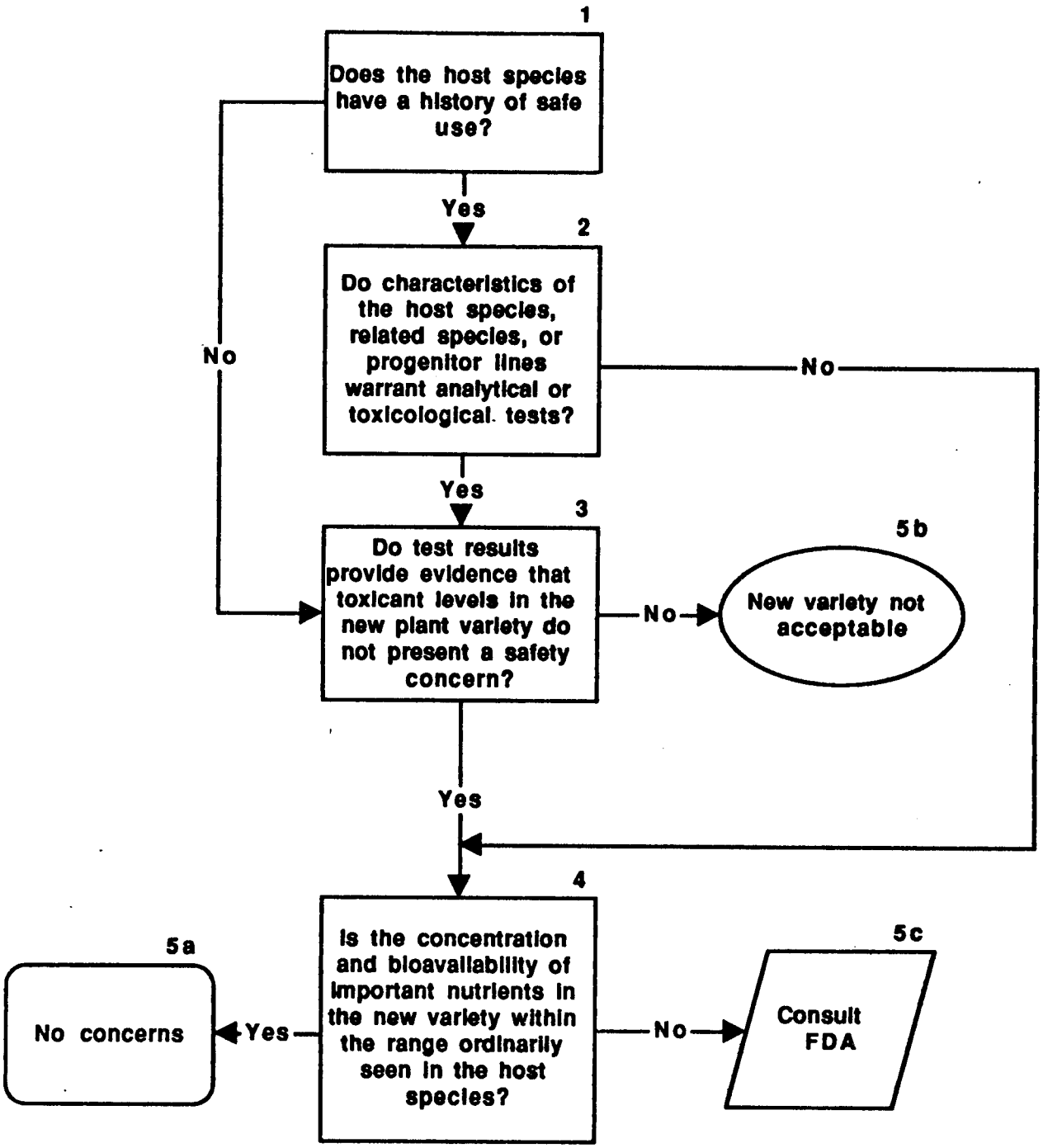

Figure 2. Safety Assessment of New Varieties: The Host Plant

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Notes to Figure 2

1—Does the host species have a history of safe use?

This guidance section is primarily designed for the development of new varieties of currently consumed food plants whose safety has been established by a history of use. If exotic species are used as hosts, testing may be needed to assure the safety and wholesomeness of the food.

2—Do characteristics of the host species, related species, or progenitor lines warrant analytical or toxicological tests?

It is not possible to establish a complete list of all toxicants that should be considered for each plant species. In general, the toxicants that are of highest concern in any particular species are those that have been documented to cause harm in normal or animal diets, or that have been found at unsafe levels in some lines or varieties of that species or related species.

In many cases, characteristic properties (such as a bitter taste associated with alkaloids) are known to accompany elevated levels of specific natural toxicants. If such characteristic provide an assurance that these toxicants have not been elevated to unsafe levels, analytical or toxicological tests may not be necessary.

3—Do test results provide evidence that toxicant levels in the new plant variety do not present a safety concern?

If a host plant or related species is known to contain toxicants whose presence must be assessed, analytical tests may be appropriate to establish that the toxicant levels are in a safe range. There is, however, a wide variation in the level of natural toxicants within and between varieties of a species, due to differences in genetic makeup and in environmental conditions during growth, harvest, and storage. Due to this natural variation, analytical tests, if necessary, should be performed using as a control the parental variety that has been grown, harvested, and stored under the same conditions as the new plant variety.

In some cases, analytical methods alone may not be available, practical, or sufficient for all toxicants whose levels are needed to be assessed. In such situations, comparative toxicological tests on the new and parental plant varieties may provide assurance that the new variety is safe. FDA encourages producers of new plant varieties to consult informally with the agency on testing protocols for whole foods when appropriate.

4—Is the concentration and bioavailability of important nutrients in the new variety within the range ordinarily seen in the host species?

If the native levels of important nutrients for which a food is widely consumed are not within the range ordinarily seen in the host species, appropriate labeling may be required. In addition, changes in bioavailability of a nutrient due to changes in form of the nutrient or the presence of increased levels of other constitutents that affect absorption or metabolism of nutrients must be considered for potential nutritional impact.

5—Endpoints in Figure 2.

5a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to the host plant will generally have been satisfied.

5b—New variety not acceptable.

This endpoint is reached when test results indicate that food derived from the new plant variety may be unsafe—e.g., if it contains unacceptable levels of toxicants.

5c—Consult FDA.

Producers should consult informally with FDA when the concentration or bioavailability of important nutrients is not within the range ordinarily seen in the host species. FDA will work with the producers on a case-by-case basis to address requirements such as labeling, or other issues relating to nutritional concerns.

E. The Donor(s)

In some cases, the donor will not have a history of safe use in food. For example, the donor may be a wild species that is related to the host plant, or may be a microorganism with no history of use in food. The potential of the donor(s) to contribute undesirable characteristics to the new plant variety should be assessed. In assessing the potential of the donor to contribute unexpected harmful substances, producers should consider attributes of the donor plant, or of fragments of genetic material from one or multiple donors, to the extent that such information is available (see Figure 3).

1. Donor Plants

Attributes of the donor plant and its progenitors, such as the following, should be considered:

1. Taxonomy.

a. Variety name.

b. Known phenotypes and relevant genotypes.

2. Other species or varieties that have previously contributed genetic information to the donor plant.

3. History of use (as applicable).

a. The part of the plant used as food.

b. The presence and identity of potentially harmful constituents such as toxicants, antinutrients, and allergens.

c. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.

2. Fragments of Donor Genetic Material

Attributes of each donor, and its progenitors when appropriate, such as the following, should be considered:

1. Taxonomy.

2. Other species or varieties that have previously contributed genetic information to the donor(s).

3. History of use (as applicable).

a. The part of the donor(s) used as food.

b. The presence and identity of potentially harmful constituents, such as toxicants, antinutrients, and allergens.

c. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.

d. The association of the transferred genetic material with harmful constituents.

4. Additional information consistent with currently accepted scientific practices, such as:

a. History and derivation of molecular constructs, such as passage through microbial hosts.

b. Known activities of any introduced regulatory sequences, such as environmental, developmental and tissue-specific effects on promoter activity.

c. The presence of extraneous open reading frames, and the potential for transcription and expression of these additional open reading frames.

Figure 3

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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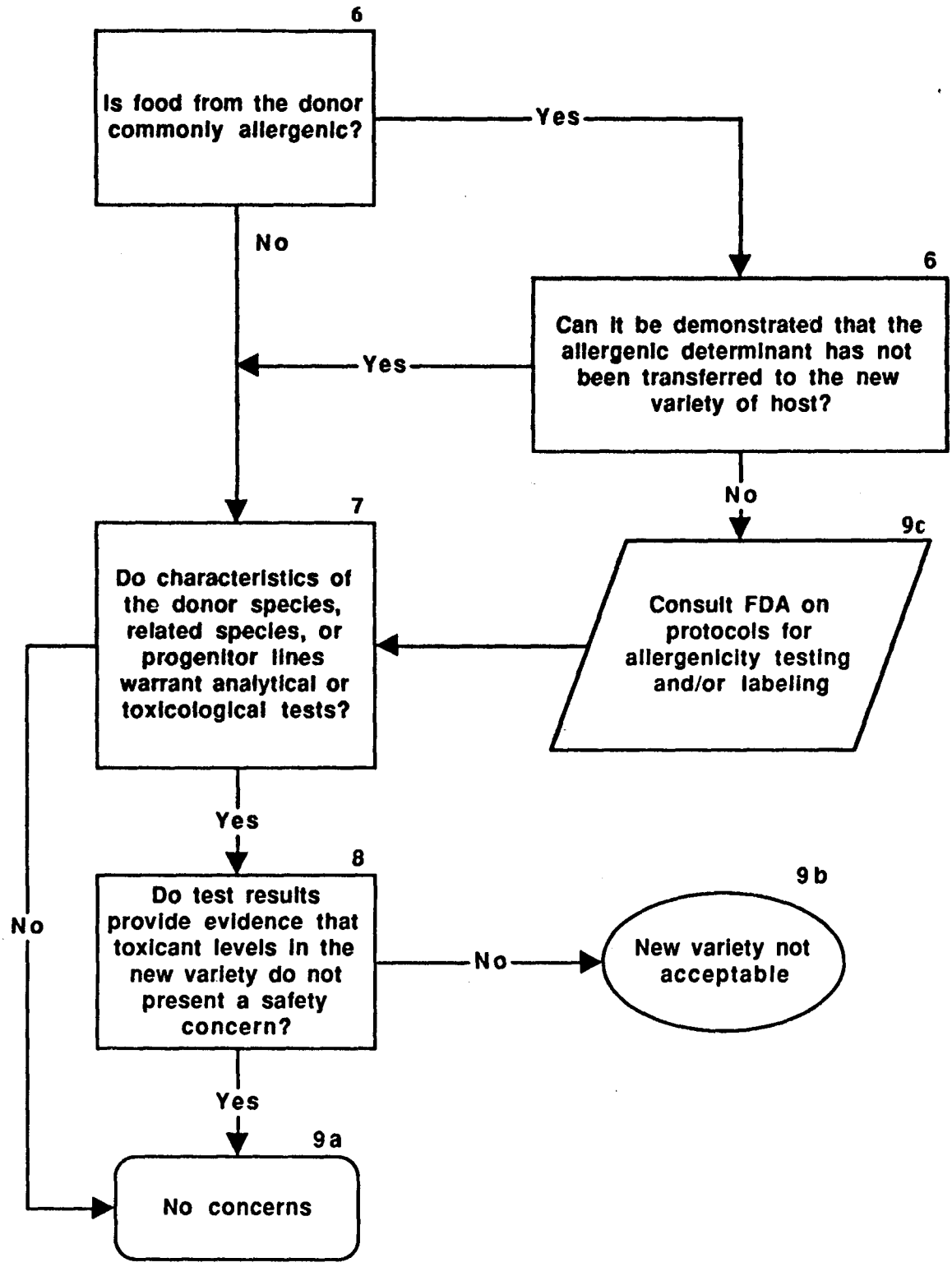

Figure 3. Safety Assessment of New Varieties: The Donor(s)

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Notes to Figure 3

6—Is food from the donor commonly allergenic? If yes, can it be demonstrated that the allergenic determinant has not been transferred to the new variety of host plant?

Some examples of foods that commonly cause an allergenic response are milk, eggs, fish, crustacea, molluscs, tree nuts, wheat, and legumes (particularly peanuts and soybeans). Allergens from these common sources may be knowingly or unknowingly transferred from a donor to a new variety of host plant. Knowledge of the identity of the allergenic determinant of the donor, coupled with appropriate knowledge of the genetic fragment that has been transferred from the donor to the new plant variety, may provide sufficient evidence that the allergenic determinant has not been transferred to the new variety of the host plant.

7—Do characteristics of the donor species, related species, or progenitor lines warrant analytical or toxicological tests?

It is possible that a toxicant present in the donor may be transferred to the host, e.g., during hybridization of a cultivated variety with a wild, poisonous relative. However, it is also possible to use a toxic donor safely. For example, a gene coding for an enzyme that is not toxic and does not yield toxic products may be isolated from pathogenic bacteria and safely transferred to a plant.

The potential that toxicants known to exist in the donor, related species, or progenitor lines will be present in the new plant variety should be addressed as described previously for the host plant (section VII.D.). Unless there is sufficient evidence that the toxicant has not been transferred to the new variety of host plant, such transfer should be assumed, and analytical and/or toxicological tests may be warranted.

8—Do test results provide evidence that toxicant levels in the new variety do not present a safety concern?

When the presence of donor-associated toxicants must be assessed, analytical or toxicological studies may provide assurance that the new variety is safe as described previously for the host species (section VII.D.). FDA encourages producers of new plant varieties to consult with the agency on testing protocols.

9—Endpoints in Figure 3.

9a—No concerns.

When this endpoint is reached, safety concerns relative to the donor will generally have been satisfied.

9b—New variety not acceptable.

This endpoint is reached when test results indicate that food derived from the new plant variety may be unsafe, e.g., if it contains unacceptable levels of toxicants.

9c—Consult FDA.

Appropriately designed tests may provide evidence that the suspected allergen in the donor was not transferred to the new plant variety, or is not allergenic in the new variety. Producers should consult informally with FDA on protocols that are designed to assess allergenicity. FDA will work with the producer on a case-by-case basis to address requirements such as labeling.

F. Substances Introduced Into the Host Plant From the Donor(s)

Safety assessment should address the specific risks associated with the new substances introduced from the donor(s) to a degree that is consistent with currently accepted scientific practices.

1. Proteins

Depending upon the circumstances, safety assessment of an introduced protein should be based on:

1. Presence and level in the food product.
2. Origin.
3. Known or suspected allergenicity.
4. Evidence of consumption in other foods at similar levels and under similar conditions of processing (e.g., eaten cooked or uncooked).
5. Effects of processing (e.g., cooking).
6. Biological function.
7. Known or potential toxicity.
8. Chemical differences and similarities to edible proteins.
9. The presence of host-specific posttranslational modifications.

Figure 4

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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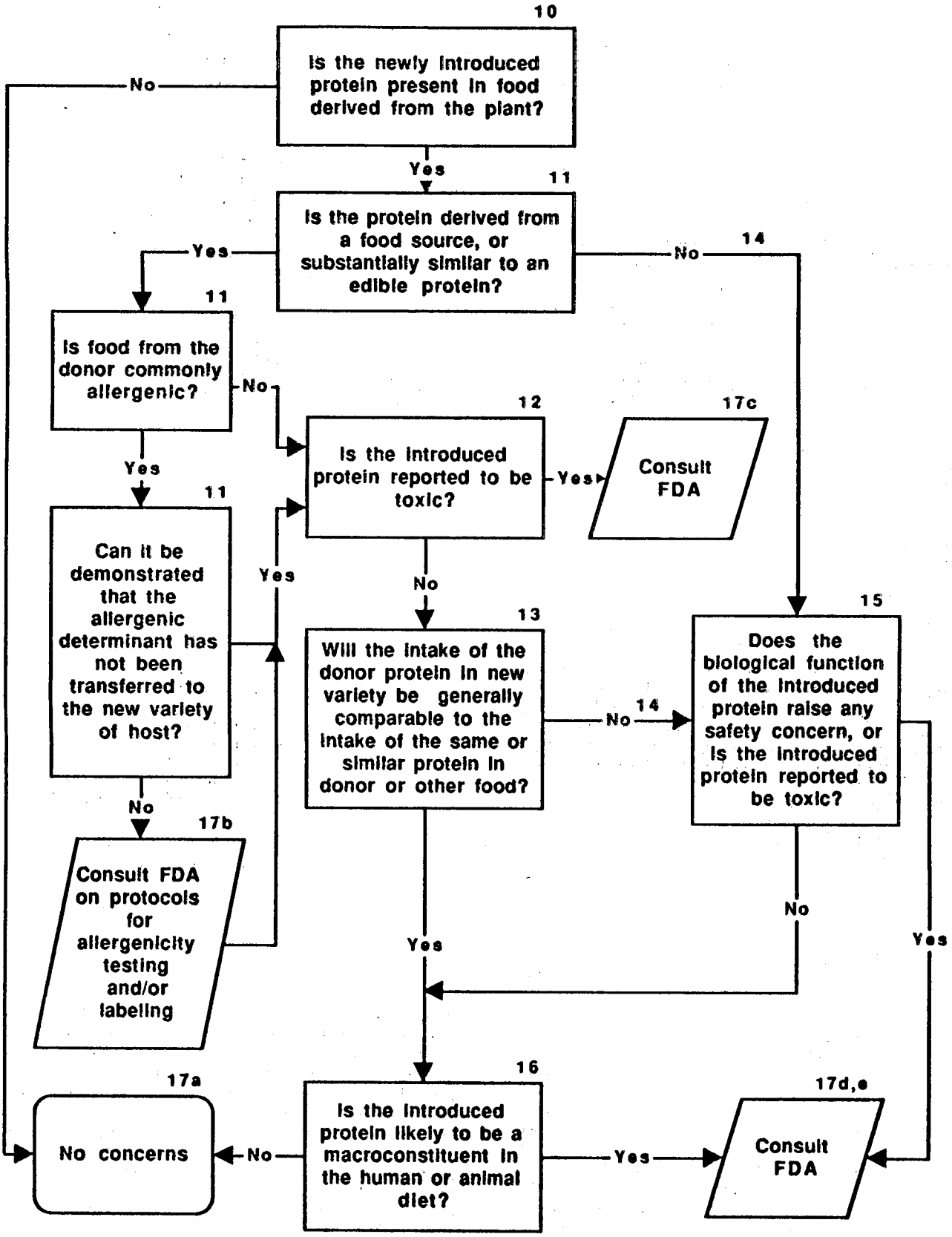

Figure 4. Safety Assessment of New Varieties: Proteins Introduced from Donor(s)

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Notes to Figure 4

10—Is the newly introduced protein present in food derived from the plant?

For example, an enzyme introduced to alter the fatty acid composition of an oil may be removed from the oil as a result of processing. Alternatively, an enzyme introduced to confer antibiotic resistance for use as a selectable marker may be present in food products.

11—If an introduced protein is derived from a food source, the question of allergenicity must be addressed in the same fashion as was discussed from the perspective of the donor as a whole.

12—Is the introduced protein that is derived from a food source, or is substantially similar to an edible protein, reported to be toxic?

For example, some lectins are toxic unless inactivated by cooking. If a protein whose safety is dependent on processing such as cooking has been transferred from a species that is commonly cooked before consumption to a species that may be eaten raw, safety questions may arise.

13—If the intake of an introduced protein that is derived from a food source, or that is substantially similar to an edible protein, is not generally comparable to the intake of the same or similar protein in the donor or other food, the biological function of the protein should be assessed.

14—The biological function of the introduced protein should be assessed if either of the following occur:

a. The introduced protein is not derived from a food source, or is not substantially similar to an edible protein; [6]

b. The intake of the introduced protein in the new variety is not comparable to the intake of the same or similar protein in the donor or other food.

15—Does the biological function of the introduced protein raise any safety concerns, or is the introduced protein reported to be toxic?

In general, proteins that function as enzymes do not raise concern [7] Exceptions include enzymes that produce substances that are not ordinarily digested and metabolized by vertebrates, or that produce toxic substances (e.g., the enzymes that convert cyanogenic glycosides to cyanide).

Other functions that could raise concern include any reported toxicity, such as known toxic activity toward vertebrates, known toxic activity toward nonvertebrates when the absence of toxic activity to vertebrates is not established, and unusual properties that indicate that the protein is significantly different from other proteins found in the diet. If the function of the protein is not known, see note 17d.

16—Is the introduced protein likely to be a macroconstituent in the human or animal diet?

From a nutritional standpoint, the amount and quality of total protein in the diet, rather than of any particular protein, is of greatest significance. However, while most individual proteins (e.g., enzymes) that might be introduced into food derived from plants will be present at relatively low concentrations, some proteins (e.g., seed storage proteins) [8] may become macroconstituents of the plant-derived food. Other proteins (e.g., enzymes used as selectable marker genes) may be introduced into many plants and therefore be consumed at a substantial level. Dietary exposure to such proteins should be considered.

17—Endpoints in Figure 4.

17a—No concerns.

When this endpoint is reached, safety concerns relative to intentionally introduced proteins will generally have been satisfied.

17b—Consult FDA: Allergens.

Producers should consult informally with FDA on protocols that are designed to assess allergenicity. FDA will work with the producer on a case-by-case basis to address requirements such as labeling.

17c—Consult FDA: Toxicity.

Producers should consult informally with FDA when a protein is reported to be toxic or when the safety of an introduced protein is dependent on processing such as cooking. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins, or whether the proteins are unacceptable in the new plant variety.

17d—Consult FDA: Function and toxicity.

Producers should consult informally with FDA on scientific issues and design of appropriate test protocols when the function of the protein raises concern or is not known, or the protein is reported to be toxic. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins.

17e—Consult FDA: Macroconstituents in the diet.

Producers should consult informally with FDA when a protein is expected to become a macroconstituent of the diet, whether as a result of its presence in high levels in one food or as a result of its use in many foods. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins.

2. Carbohydrates

Safety assessment of a new or modified carbohydrate should be based on the nature of the carbohydrate or modification.

Figure 5

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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[6] The issue of potential allergenicity of any new protein (as opposed to the allergenicity of a protein derived from a known source of allergens) is frequently raised. FDA recognizes that routine procedures for testing foods derived from new plant varieties for the presence of unknown allergens are not currently available. If the donor has no history of use in food, the issue of allergenicity cannot be addressed at this time. Comparison of gene sequences to data banks of known allergens may become increasingly useful as the information on such proteins expands. FDA invites comments on methods that may be available to address the issue of allergenicity of new proteins in foods.

[7] Pariza and Foster (Ref. 7) note that very few toxic agents have enzymatic properties. Exceptions include diphtheria toxin and certain enzymes in the venom of poisonous snakes.

[8] The nutritional content of seed storage proteins from some crops is particularly important in the case of animal feed, where one crop may furnish a substantial portion of the diet.

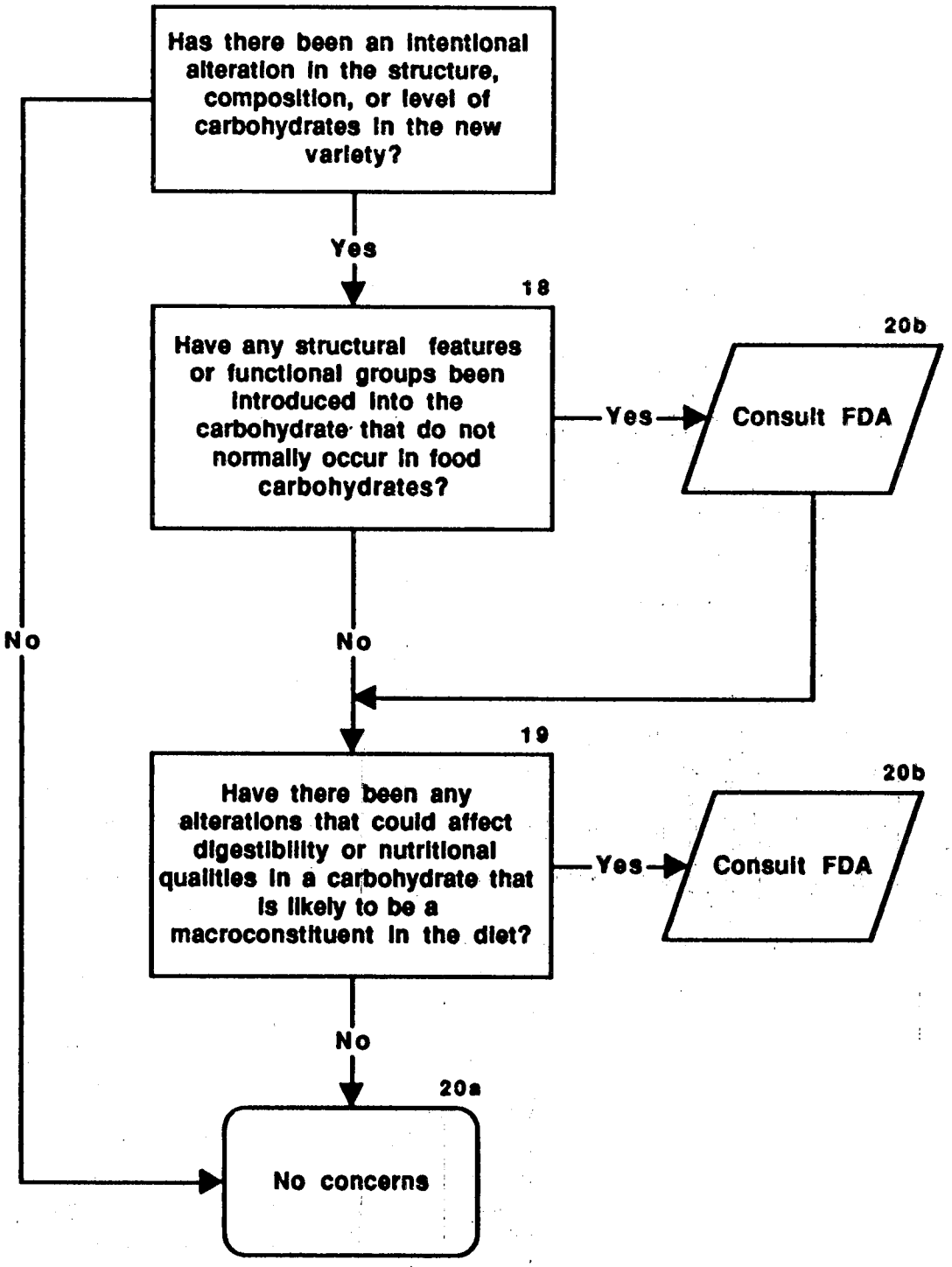

Figure 5. Safety Assessment of New Varieties: New or Modified Carbohydrates

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Notes to Figure 5

18—Have any structural features or functional groups been introduced into the carbohydrate that do not normally occur in food carbohydrates?

For example, developments that affect carbohydrates will frequently be modifications of food starches, presumably affecting the content of amylose and amylopectin, as well as the branching of amylopectin. Such modified starches are likely to be functionally and physiologically equivalent to starches commonly found in food and thus would not suggest any specific safety concerns. However, if functional groups or structural features that normally do not occur in food carbohydrates are introduced, such modifications should be evaluated with respect to any safety concerns that may arise.

19—Have there been any alterations that could affect digestibility or nutritional qualities in a carbohydrate that is likely to be a macroconstituent in the diet?

If a vegetable or a fruit is modified to produce high levels of an indigestible carbohydrate that normally occurs at very low levels, or to convert a normally digestible carbohydrate to an indigestible form, nutritional questions may arise.

20—Endpoints in Figure 5.

20a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to intentional modifications of food carbohydrates will generally have been satisfied.

20b—Consult FDA.

Producers may consult informally with FDA on scientific issues. FDA will determine on a case-by-case basis whether it will review the food additive status of these carbohydrates, and will work with the sponsor on a case-by-case basis to address requirements such as labeling.

3. Fats and Oils

Safety assessment of a new or modified fat or oil should be based on its composition and the presence of any unusual components at levels that would cause safety concern.

Figure 6

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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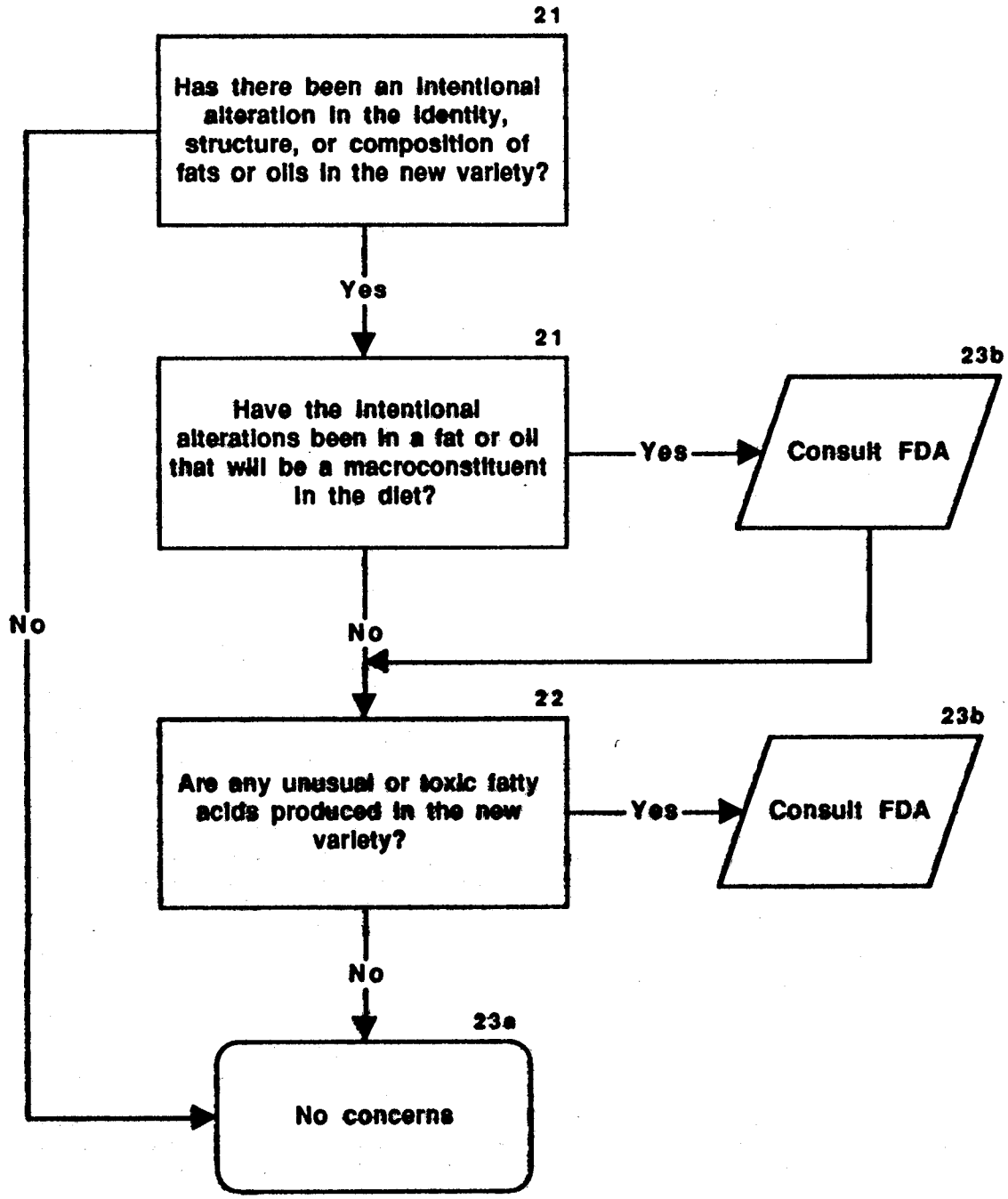

Figure 6. Safety Assessment of New Varieties: New or Modified Fats or Oils

BILLING CODE 4160-01-C

Notes to Figure 6

21—Has there been an intentional alteration in the identity, structure, or composition of fats or oils that are likely to be a macroconstituent in the diet?

Some alterations in the composition or structure of fats and oils, such as an alteration in the ratio of saturated to unsaturated fatty acids, may have significant nutritional consequences, or result in marked changes in digestibility. Other changes may produce a fat or oil that has been altered such that it is no longer representative of fats and oils from the host species.

22—Are any unusual or toxic fatty acids produced in the new variety?

For example, safety questions may arise as a result of the presence of fatty acids with chain length greater than C–22, fatty acids with cyclic substituents, fatty acids with functional groups not normally present in dietary fats and oils, and fatty acids of known toxicity (e.g., erucic acid).

23—Endpoints in Figure 6.

23a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to intentional modifications of fats and oils will generally have been satisfied.

23b—Consult FDA.

Producers may consult informally with FDA on scientific issues. FDA will determine on a case-by-case basis whether it will review the food additive status of these fats or oils, and will work with the sponsor on a case-by-case basis to address requirements such as labeling.

G. Toxicology

Feeding studies or other toxicological tests may be warranted when the characteristics of the plant or the nature of the modification raise safety concerns that cannot be resolved by analytical methods. FDA recognizes that feeding studies on whole foods have limited sensitivity because of the inability to administer exaggerated doses. Because of the difficulty of designing meaningful studies, FDA encourages companies to consult informally with the agency about test protocols.

H. Other Information

The information described below is not directly addressed in the flow charts but should be considered during the development of new plant varieties.

1. Nucleic Acids

Introduced nucleic acids, in and of themselves, do not raise safety concerns. Thus, for example, the introduction of a gene encoding an anti-sense ribonucleic acid (RNA) would not raise concerns about either the gene or the anti-sense RNA. Any safety considerations would focus on the intended effects of the anti-sense RNA. Hence, continuing the example, if the anti-sense RNA were used to suppress an enzyme, then just as for any other method intended to suppress an enzyme, such as deletion or nonsense mutations, the metabolic effects on the host plant of such enzyme suppression should be considered at the conceptual stage of development and monitored, when appropriate and feasible.

2. Metabolic Considerations

The effects of an intentional alteration of a biochemical pathway should be considered at the conceptual stage of development, and monitored when appropriate and feasible. For example, are there any toxic effects of a metabolic imbalance with respect to enzyme substrate depletion and product accumulation? Are any auxiliary pathways likely to be affected?

3. Stability

The genetic stability of the new plant variety and the inheritance of the introduced genetic material as a single Mendelian trait are important safety considerations. A safety assessment of food derived from early generations of the new variety may not be valid if the new genetic material is expressed at substantially different levels in subsequent generations. Factors that favor stability include a minimum number of copies of the introduced genetic material, and insertion at a single site.

I. Future Workshop on Scientific Issues

FDA recognizes the desirability of establishing consensus within the industry, the scientific community, and the public on the agency's scientific assessment approach to food safety presented in this guidance section. For this reason, FDA plans to announce, in a future **Federal Register** notice, a workshop to discuss specific scientific issues. The notice announcing the workshop will include a description of the scientific issues to be discussed. FDA invites comment on topics that might be addressed at such a workshop.

VIII. Environmental Consideration: Applicability of NEPA

NEPA requires FDA to consider in its decisionmaking the environmental impact of its major Federal actions that significantly affect the quality of the human environment. The promulgation of a food additive regulation is an agency action that ordinarily triggers the NEPA requirement for development of an environmental assessment (21 CFR 25.22(a)(10)) and, if the agency does not make a finding of no significant environmental impact, an environmental impact statement is prepared (21 CFR 25.21(b)).

The Council on Environmental Quality (CEQ) regulations (40 CFR 1500 through 1508) provide that in complying with NEPA, an agency should avoid unnecessary duplication and should tier its NEPA statements with those of other agencies to eliminate repetitive discussions of the same issues and to focus on the actual issues ripe for decision at each level of environmental review (40 CFR 1502.20 and 1508.28).

Other agencies, particularly USDA and EPA, may prepare NEPA and other environmental documentation before products are presented to FDA for a decision. FDA intends to rely on such documentation to the maximum extent possible.

Under regulations administered by the Animal and Plant Health Inspection Service (APHIS) in USDA (7 CFR part 340), the majority of plants developed by recombinant DNA techniques that are being commercially developed have been considered "regulated articles." The action that results in a permit for introduction of a regulated article into the environment is subject to NEPA review. At some stage of research and development of a regulated article, an interested party will request from APHIS a determination of the article's regulatory status. APHIS has informed FDA that when APHIS receives a petition or other request it intends to consult with other agencies. This should enable FDA to identify the type of data that would be useful if any subsequent environmental review is to be prepared for actions under FDA jurisdiction.

EPA has authority, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*), to regulate all pesticides, no matter how they are made or their mode of action. Under the act, EPA has authority to regulate pesticide residues in foods. Any relevant review that EPA conducts under FIFRA, the act, or any other of its statutes, involving an assessment of potential effects on human health and the environment will be available to FDA.

FDA intends to work closely with USDA and EPA to minimize duplication of environmental reviews. The agency will, to the extent possible, invoke the tiering provisions in the CEQ regulations and, in FDA's environmental assessments, rely on APHIS NEPA reviews and other such documents, as well as relevant environmental documents considered by EPA. Further,

FDA will provide informal guidance on environmental issues to assist individuals who are preparing food additive petitions to meet FDA's requirements for environmental assessments.

FDA does not consider that the activities it may undertake with respect to foods from new plant varieties other than promulgation of food additive regulations, such as consultation with producers on safety issues and providing advice on the regulatory status of foods from new plant varieties, will constitute agency action under NEPA.

IX. Coordination With EPA: Pesticide Considerations

Questions have been raised concerning whether FDA or EPA would have jurisdiction when plants are modified to express pesticidal substances. FDA and EPA are agreed that substances that are pesticides as defined by FIFRA (7 U.S.C. section 136(u)), are subject to EPA's regulatory authority. The agencies also agree that FDA's authority under the act extends to any nonpesticide substance that may be introduced into a new plant variety and that is expected to become a component of food.

EPA and FDA are aware that there may be cases in which the jurisdictional responsibility for a substance is not clear. Because pesticides, as defined by FIFRA, are subject to EPA's jurisdiction, the agencies encourage producers who have such questions to contact EPA. FDA and EPA intend to consult closely on such jurisdictional questions, as well as on scientific matters where consultation will be helpful in resolving safety questions.

The agencies are also aware that, in some circumstances, evaluation of a particular substance introduced into a plant may require the expertise of both EPA and FDA. Both agencies agree that EPA will address under its regulatory jurisdiction the food safety issues associated with the pesticide, including marker genes used to confirm the presence of the pesticidal gene. Any food safety questions beyond those associated with the pesticide, such as those raised by unexpected or unintended compositional changes, are under FDA's jurisdiction and should be addressed under the policy set forth elsewhere in this notice.

Based upon the agencies' current knowledge, examples of substances that fall under FDA's authority include: (1) Substances intended to alter the nutritional composition of the food (e.g., amino acids or carbohydrates); (2) substances intended to enhance the plant's resistance to chemical herbicides (e.g., bromoxynil, glyphosate, and sulfonylurea); and (3) substances intended to alter the flavor or the texture of the food.

Similarly, based upon the agencies' current knowledge of new plant varieties being developed using the new technologies of gene transfer, EPA is in the process of evaluating how or if it will exert its oversight for the following examples subject to its jurisdiction under FIFRA and therefore not under FDA's jurisdiction: (1) Substances that are intended to kill insects (e.g., *Bacillus thuringiensis* delta-endotoxin);

(2) Substances intended to protect plants from viral, fungal, or bacterial infection (e.g., cecropin); and (3) substances that are plant regulators and thus "pesticides" under FIFRA.

X. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This action is intended to provide guidance to developers by describing the scientific considerations for the safe development of foods derived from new plant varieties.

XI. Comments

Interested persons may, on or before August 27, 1992, submit to the Dockets Management Branch (address above) written comments regarding this notice. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Anonymous, "Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification," International Food Biotechnology Council, Regulatory Toxicology and Pharmacology, Vol. 12, No. 3, Part 2 of 2 Parts, New York, December 1990.

2. Letter, Hopkins, D. D., R. J. Goldburg, and S. A. Hirsch to Dr. David Kessler, September 30, 1991, and enclosure, "A Mutable Feast: Assuring Food Safety in the Era of Genetic Engineering."

3. Letter, Richard D. Godown to James H. Maryanski, January 3, 1992; Letter, W. Douglas Crabb to Fred R. Shank, January 24, 1992.

4. Comments to Docket No. 90A-0416, **Federal Register**, May 1, 1991 (56 FR 20004).

5. Dale, E. C. and D. W. Ow, "Gene Transfer with Subsequent Removal of the Selection Gene from the Host Genome," Proceedings of the National Academy of Sciences USA, 88:10558-10562, 1991.

6. Anonymous, "Strategies for Assessing the Safety of Foods Produced by Biotechnology," World Health Organization, Geneva, 1991.

7. Pariza, M. W. and E. M. Foster, "Determining the Safety of Enzymes Used in Food Processing," Journal of Food Protection, 46:453-468, 1983.

Dated: April 2, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 92-12660 Filed 5-26-92; 3:57 pm]

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FDA 2001 Draft Guidance

DRAFT Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering; Draft Guidance

Contains Nonbinding Recommendations

Draft released for comment January 2001

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with Docket Number 00D-1598. For questions regarding this draft document contact Catalina Ferre-Hockensmith, (202) 205-4168.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

Contains Nonbinding Recommendations

Guidance for Industry
Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering
Draft Guidance

This draft guidance represents FDA's current thinking on voluntary labeling of foods indicating whether foods have or have not been developed using bioengineering. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of applicable statutes and regulations. The draft guidance is being distributed for comment purposes in accordance with FDA's Good Guidance Practices (65 FR 56468, September 19, 2000).

BACKGROUND

In the Federal Register of May 29, 1992 (57 FR 22984), FDA published its "Statement of Policy: Foods Derived from New Plant Varieties" (the 1992 policy). The 1992 policy applies to foods developed from new plant varieties, including varieties that are developed using recombinant deoxyribonucleic acid (rDNA) technology (which is often referred to as "genetic engineering" or "biotechnology"). This guidance document refers to foods derived from plant varieties that are developed using rDNA technology as "bioengineered foods." In addition, because the Federal Food Drug, and Cosmetic Act (the act) defines food as articles used for food or drink for man or other animals, this guidance document applies to animal feeds as well as to human foods. The 1992 policy provides guidance to industry on scientific and regulatory issues related to bioengineered foods and solicited written comments from interested persons. The policy includes guidance on questions to be answered by developers of foods from new plant varieties, to ensure that the new products are safe and comply with applicable legal requirements. It also encourages continuation of the general practice of the food industry to consult with the agency about the safety of new foods,

e.g., bioengineered foods.

In the 1992 policy, FDA also addresses the labeling of foods derived from new plant varieties, including plants developed by bioengineering. The 1992 policy does not establish special labeling requirements for bioengineered foods as a class of foods. The policy states that FDA has no basis for concluding that bioengineered foods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding.

To fully understand the agency's mandate and authority in requiring labeling of foods, one must refer to the Federal Food, Drug, and Cosmetic Act (the act) to determine the extent to which the agency is charged with governing labeling of foods. Section 403 governs the labeling of foods. Under section 403(a)(1), a food is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the act provides additional guidance on how labeling may be misleading. It states that labeling is misleading if it fails to reveal facts that are material in light of representations made or suggested in the labeling, or material with respect to consequences that may result from the use of the food to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual. While the legislative history of section 201 (n) contains little discussion of the word "material," there is precedent to guide the agency in its decision regarding whether information on a food is in fact material. Historically, the agency has generally interpreted the scope of the materiality concept to mean information about the attributes of the food itself. FDA has required special labeling on the basis of it being "material" information in cases where the absence of such information may: 1) pose special health or environmental risks (e.g., warning statement on protein products used in very low calorie diets); 2) mislead the consumer in light of other statements made on the label (e.g., requirement for quantitative nutrient information when certain nutrient content claims are made about a product); or 3) in cases where a consumer may assume that a food, because of its similarity to another food, has nutritional, organoleptic, or functional characteristics of the food it resembles when in fact it does not (e.g., reduced fat margarine not suitable for frying).

Although the 1992 policy does not require special labeling for bioengineered foods, the agency advised in that policy that labeling requirements that apply to foods in general also apply to foods produced using biotechnology. Section 403(i) of the act requires that each food bear a common or usual name or, in the absence of such a name, an appropriately descriptive term. In addition, under section 201(n), the label of the food must reveal all material facts about the food. Thus:

- If a bioengineered food is significantly different from its traditional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference.

- If an issue exists for the food or a constituent of the food regarding how the food is used or consequences of its use, a statement must be made on the label to describe the issue.

- If a bioengineered food has a significantly different nutritional property, its label must reflect the difference.

- If a new food includes an allergen that consumers would not expect to be present based on the name of the food, the presence of that allergen must be disclosed on the label.

In the Federal Register of April 28, 1993 (58 FR 25837), the agency requested data and information on certain labeling issues that had arisen from the labeling guidance in the 1992 policy. In 1999, the agency announced that it would hold three public meetings (64 FR 57470; October 25, 1999). The purpose of those meetings was for the agency to share its current approach and experience over the previous five years regarding bioengineered foods, to solicit views on whether FDA's policies should be modified, and to gather information to be used to assess the most appropriate means of providing information to the public about bioengineered products in the food supply. The agency received more than 50,000 written comments about its policy regarding safety and labeling of bioengineered foods. The theme related to labeling in those comments and the testimony at the meetings was that there are very strongly held but divergent views as to whether bioengineered foods should be required to bear special labeling. However, there was general agreement that providing more information to consumers about bioengineered foods would be useful. A number of comments supported the need for guidance from FDA regarding appropriate ways that industry could voluntarily provide information on a food label about bioengineering.

FDA has reviewed information in the comments received in response to the 1992 policy and the 1993 information request as well as the comments from the 1999 meetings. Most of the comments that addressed labeling requested mandatory disclosure of the fact that the food or its ingredients was bioengineered or was produced from bioengineered food. However, these comments did not provide data or other information regarding consequences to consumers from eating the foods or any other basis for FDA to find under section 201(n) of the act that such a disclosure was a material fact. Many of the comments expressed concern about possible long term consequences from consuming bioengineered foods, but they did not contend that any of the bioengineered foods already on the market have adverse health effects. The comments were mainly expressions of concern about the unknown. The agency is still not aware of any data or other information that would form a basis for concluding that the fact that a food or its ingredients was produced using bioengineering is a material fact that must be disclosed under sections 403(a) and 201(n) of the act. FDA is therefore reaffirming its decision to not require special labeling of all bioengineered foods.

The agency is providing the following guidance to assist manufacturers who wish to voluntarily label their foods as being made with or without the use of bioengineered ingredients. While the use of bioengineering is not a material fact, many consumers are interested in the information, and some manufacturers may want to respond to this consumer desire. The guidance was developed using information from the comments and from focus groups, as well as other resources, and is intended to help ensure that labeling is truthful and not misleading.

GUIDANCE

In determining whether a food is misbranded, FDA would review label statements about the use of bioengineering to develop a food or its ingredients under sections 403(a) and 201(n) of the act. Under section 403(a) of the act, a food is misbranded if statements on its label or in its labeling are false or misleading in any particular. Under section 201(n), both the presence and the absence of information are relevant to whether labeling is misleading. That is, labeling may be misleading if it fails to disclose facts that are material in light of representations made about a product or facts that are material with respect to the consequences that may result from use of the product. In determining whether a statement that a food is or is not genetically engineered is misleading under sections 201(n) and 403(a) of the act, the agency will take into account the entire label and

labeling.

Statements about foods developed using bioengineering

FDA recognizes that some manufacturers may want to use informative statements on labels and in labeling of bioengineered foods or foods that contain ingredients produced from bioengineered foods. The following are examples of some statements that might be used. The discussion accompanying each example is intended to provide guidance as to how similar statements can be made without being misleading.

- "Genetically engineered" or "This product contains cornmeal that was produced using biotechnology."

The information that the food was bioengineered is optional and this kind of simple statement is not likely to be misleading. However, focus group data indicate that consumers would prefer label statements that disclose and explain the goal of the technology (why it was used or what it does for/to the food) (Ref. 1). Consumers also expressed some preference for the term "biotechnology" over such terms as "genetic modification" and "genetic engineering" (Ref. 1).

- "This product contains high oleic acid soybean oil from soybeans developed using biotechnology to decrease the amount of saturated fat."

This example includes both required and optional information. As discussed above in the background section, when a food differs from its traditional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference. Because this soybean oil contains more oleic acid than traditional soybean oil, the term "soybean oil" no longer adequately describes the nature of the food. Under section 403(i) of the act, a phrase like "high oleic acid" would be required to appear as part of the name of the food to describe its basic nature. The statement that the soybeans were developed using biotechnology is optional. So is the statement that the reason for the change in the soybeans was to reduce saturated fat.

- "These tomatoes were genetically engineered to improve texture."

In this example, the change in texture is a difference that may have to be described on the label. If the texture improvement makes a significant difference in the finished product, sections 201(n) and 403(a)(1) of the act would require disclosure of the difference for the consumer. However, the statement must not be misleading. The phrase "to improve texture" could be misleading if the texture difference is not noticeable to the consumer. For example, if a manufacturer wanted to describe a difference in a food that the consumer would not notice when purchasing or consuming the product, the manufacturer should phrase the statements so that the consumer can understand the significance of the difference. If the change in the tomatoes was intended to facilitate processing but did not make a noticeable difference in the processed consumer product, a phrase like "to improve texture for processing" rather than "to improve texture" should be used to ensure that the consumer is not misled. The statement that the tomatoes were genetically engineered is optional.

- "Some of our growers plant tomato seeds that were developed through biotechnology to increase crop yield."

The entire statement in this example is optional information. The fact that there was increased yield does not affect the characteristics of the food and is therefore not necessary on the label to adequately describe the food for the consumer. A phrase like "to increase yield" should only be included where there is substantiation that there is in fact the stated difference.

Where a benefit from a bioengineered ingredient in a multi-ingredient food is described, the statement should be worded so that it addresses the ingredient and not the food as a whole; for example, "This product contains high oleic acid soybean oil from soybeans produced through biotechnology to decrease the level of saturated fat." In addition, the amount of the bioengineered ingredient in the food may be relevant to whether the statement is misleading. This would apply especially where the bioengineered difference is a nutritional improvement. For example, it would likely be misleading to make a statement about a nutritionally improved ingredient on a food that contains only a small amount of the ingredient, such that the food's overall nutritional quality would not be significantly improved.

FDA reminds manufacturers that the optional terms that describe an ingredient of a multi-ingredient food as bioengineered should not be used in the ingredient list of the multi-ingredient food. Section 403(i)(2) of the act requires each ingredient to be declared in the ingredient statement by its common or usual name. Thus, any terms not part of the name of the ingredient are not permitted in the ingredient statement. In addition, 21 CFR 101.2(e) requires that the ingredient list and certain other mandatory information appear in one place without other intervening material. FDA has long interpreted any optional description of ingredients in the ingredient statement to be intervening material that violates this regulation.

Statements about foods that are not bioengineered or that do not contain ingredients produced from bioengineered foods

Terms that are frequently mentioned in discussions about labeling foods with respect to bioengineering include "GMO free" and "GM free." "GMO" is an acronym for "genetically modified organism" and "GM" means "genetically modified." Consumer focus group data indicate that consumers do not understand the acronyms "GMO" and " GM" and prefer label statements with spelled out words that mean bioengineering (Ref. 1).

Terms like "not genetically modified" and "GMO free," that include the word "modified" are not technically accurate unless they are clearly in a context that refers to bioengineering technology. "Genetic modification" means the alteration of the genotype of a plant using any technique, new or traditional. "Modification" has a broad context that means the alteration in the composition of food that results from adding, deleting, or changing hereditary traits, irrespective of the method. Modifications may be minor, such as a single mutation that affects one gene, or major alterations of genetic material that affect many genes. Most, if not all, cultivated food crops have been genetically modified. Data indicate that consumers do not have a good understanding that essentially all food crops have been genetically modified and that bioengineering technology is only one of a number of technologies used to genetically modify crops. Thus, while it is accurate to say that a bioengineered food was "genetically modified," it likely would be inaccurate to state that a food that had not been produced using biotechnology was "not genetically modified" without clearly providing a context so that the consumer can understand that the statement applies to bioengineering.

The term "GMO free" may be misleading on most foods, because most foods do not contain

organisms (seeds and foods like yogurt that contain microorganisms are exceptions). It would likely be misleading to suggest that a food that ordinarily would not contain entire "organisms" is "organism free."

There is potential for the term "free" in a claim for absence of bioengineering to be inaccurate. Consumers assume that "free" of bioengineered material means that "zero" bioengineered material is present. Because of the potential for adventitious presence of bioengineered material, it may be necessary to conclude that the accuracy of the term "free" can only be ensured when there is a definition or threshold above which the term could not be used. FDA does not have information with which to establish a threshold level of bioengineered constituents or ingredients in foods for the statement "free of bioengineered material." FDA recognizes that there are analytical methods capable of detecting low levels of some bioengineered materials in some foods, but a threshold would require methods to test for a wide range of genetic changes at very low levels in a wide variety of foods. Such test methods are not available at this time. The agency suggests that the term "free" either not be used in bioengineering label statements or that it be in a context that makes clear that a zero level of bioengineered material is not implied. However, statements that the food or its ingredients, as appropriate, was not developed using bioengineering would avoid or minimize such implications. For example,

- "We do not use ingredients that were produced using biotechnology;"
- "This oil is made from soybeans that were not genetically engineered;" or
- "Our tomato growers do not plant seeds developed using biotechnology."

A statement that a food was not bioengineered or does not contain bioengineered ingredients may be misleading if it implies that the labeled food is superior to foods that are not so labeled. FDA has concluded that the use or absence of use of bioengineering in the production of a food or ingredient does not, in and of itself, mean that there is a material difference in the food. Therefore, a label statement that expresses or implies that a food is superior (e.g., safer or of higher quality) because it is not bioengineered would be misleading. The agency will evaluate the entire label and labeling in determining whether a label statement is in a context that implies that the food is superior.

In addition, a statement that an ingredient was not bioengineered could be misleading if there is another ingredient in the food that was bioengineered. The claim must not misrepresent the absence of bioengineered material. For example, on a product made largely of bioengineered corn flour and a small amount of soybean oil, a claim that the product "does not include genetically engineered soybean oil" could be misleading. Even if the statement is true, it is likely to be misleading if consumers believe that the entire product or a larger portion of it than is actually the case is free of bioengineered material. It may be necessary to carefully qualify the statement in order to ensure that consumers understand its significance.

Further, a statement may be misleading if it suggests that a food or ingredient itself is not bioengineered, when there are no marketed bioengineered varieties of that category of foods or ingredients. For example, it would be misleading to state "not produced through biotechnology" on the label of green beans, when there are no marketed bioengineered green beans. To not be misleading, the claim should be in a context that applies to the food type instead of the individual manufacturer's product. For example, the statement "green beans are not produced using biotechnology" would not imply that this manufacturer's product is different from other green

beans.

Substantiation of label statements

A manufacturer who claims that a food or its ingredients, including foods such as raw agricultural commodities, is not bioengineered should be able to substantiate that the claim is truthful and not misleading. Validated testing, if available, is the most reliable way to identify bioengineered foods or food ingredients. For many foods, however, particularly for highly processed foods such as oils, it may be difficult to differentiate by validated analytical methods between bioengineered foods and food ingredients and those obtained using traditional breeding methods. Where tests have been validated and shown to be reliable they may be used. However, if validated test methods are not available or reliable because of the way foods are produced or processed, it may be important to document the source of such foods differently. Also, special handling may be appropriate to maintain segregation of bioengineered and nonbioengineered foods. In addition, manufacturers should consider appropriate recordkeeping to document the segregation procedures to ensure that the food's labeling is not false or misleading. In some situations, certifications or affidavits from farmers, processors, and others in the food production and distribution chain may be adequate to document that foods are obtained from the use of traditional methods. A statement that a food is "free" of bioengineered material may be difficult to substantiate without testing. Because appropriately validated testing methods are not currently available for many foods, it is likely that it would be easier to document handling practices and procedures to substantiate a claim about how the food was processed than to substantiate a "free" claim.

FDA has been asked about the ability of organic foods to bear label statements to the effect that the food (or its ingredients) was not produced using biotechnology. On December 21, 2000, the Agriculture Marketing Service of the U.S. Department of Agriculture (USDA) published final regulations on procedures for organic food production (National Organic Program final rule; 65 FR 80548). That final rule requires that all but the smallest organic operations be certified by a USDA accredited agent and lays out the requirements for organic food production. Among those requirements is that products or ingredients identified as organic must not be produced using biotechnology methods. The national organic standards would provide for adequate segregation of the food throughout distribution to assure that non-organic foods do not become mixed with organic foods. The agency believes that the practices and record keeping that substantiate the "certified organic" statement would be sufficient to substantiate a claim that a food was not produced using bioengineering.

References

1. Levy, A.S., Derby, B.M., "Report on Consumer Focus Groups on Biotechnology", Consumer Studies Team, Center for Food Safety and Nutrition, Food and Drug Administration, Washington, D.C., 2000

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Links on this page:

CQ Congressional Transcripts, Testimony of Dr. Margaret Hamburg, Commissioner of FDA, March 27, 2014

CQ CONGRESSIONAL TRANSCRIPTS
Congressional Hearings
March 27, 2014 - Final

House Appropriations Subcommittee on Agriculture, Rural Development FDA and Related Agencies Holds Hearing on President Obama's Proposed Fiscal 2015 Budget Request for the Food and Drug Administration

LIST OF PANEL MEMBERS AND WITNESSES

ADERHOLT:

Well, good morning. The subcommittee will come to order. I thank all of you for being here this morning and for being at our hearing to discuss FDA's FY 15 budget request. As I have mentioned on all the previous budget hearings that we've had thus far, the subcommittee is conducting its work with three primary things in mind.

Number one, ensuring the proper use of funds through the Committee's oversight responsibility; ensuring that the appropriate level of regulation to protect producers and the public, which will be number two; number three, ensuring the taxpayers funds are targeted to the most vital programs. We will be reviewing FDA's budget this morning and a lot of these things as we move forward.

I would like to welcome to the subcommittee this morning, Dr. Margaret Hamburg, who is the commissioner of the Food and Drug Administration. Also having to join us today is Mr. Bill William Tootle, who is the director of Office of Budget, FDA, and Mr. Norris Cochran, who is the deputy assistant secretary for the Department of Health and Human Services. So, welcome all of you and I'm glad to have here this morning.

I thank everyone in this room or anyone who's even viewing this hearing this morning, whether they're on C-SPAN or otherwise, would be touched or touched someway by FDA. If not today, they will be tomorrow. The agency's works from the food safety to the safety of cosmetics to human drugs plays a critical role in our health and welfare. I now believe I can speak for all of us that are here in the dais and all those who will be joining us at the dais as we -- as we get sorted this morning that we appreciate your service, your dedication, and all those that you work with at FDA.

Most of the public and many of our colleagues here in Congress are often surprised to learn that FDA regulates 20 to 25 percent of every consumer dollar spent on products in the United States. Your work can contribute to saving lives on the one hand and on the other hand, your regulatory decisions can mean the life or death to a business across the nation and the world.

The extensive involvement of FDA, in so many aspects of our daily life and the economy as a whole, carries both benefits and risks. Because of your Agency's influence on so much of our personal and professional lives, it is incumbent upon this subcommittee to ensure that FDA is making sound financial and regulatory decisions throughout the year and not just over the course of the next few hours here this morning.

FDA's responsibilities have grown over the past few years via the global marketplace and by way of

LOWEY:

With limited time, I'm just going to ask one more question, but I'm particularly interested in with the imported food issue as well. The Congressional Research Service says that an estimated 60 to 70 percent of all U.S. process foods probably came -- contain some genetically-engineered material because there are so much corn and soybeans in the process foods with it.

I strongly believe that consumers have the right to know what they're eating. I know that FDA has said it supports voluntary labeling, but I would support mandatory labeling of foods as to whether they are genetically modified. Would you review for us how FDA currently approaches GE labeling?

HAMBURG:

Well, as you noted, we have supported voluntary labeling and we put a proposed guidance with respect to plant-based genetically modified foods and we hope to finalize that soon. With respect to mandatory labeling, the way that over many, many years FDA has interpreted the law and it has been supported by the court is that mandatory labeling, you know, really is appropriate and required when there is a false claim or misbranding that the fact that food contains GE materials does not constitute a material change in the product unless -- you know, material change meaning in the nutritional content, the performance of the food, the taste, the aroma, et cetera, if...

LOWEY:

Are you convinced that's the case?

HAMBURG:

You know, I -- this is an area that obviously is very much on the minds of many Americans in the subject of lot of discussion and some controversy. There have been, you know, a lot of very credible scientific organizations that have looked hard at this issue over a long period of time. We have not seen evidence of safety risks associated with genetically-modified foods in terms of health. Others have looked at environmental issues.

It's an area that deserves further discussion and further study. We do think that a voluntary approach to labeling makes a lot of sense because for people who have the desire the avoid GE food, this would give them the opportunity to choose. But from a scientific and safety assessment point of view, we do not currently believe that the fact that there has been genetic modification of a food product makes it a material change to the product in terms of its nutritional or other qualities unless -- and there are some instances.

For example, if their genetic engineering approach introduced a potential toxin that wouldn't normally be in that food product such as a peanut toxin into an oil or tomato or whatever, then we would require labeling of the potential for exposure to this toxin because that would be a material change that would create a health or safety concern.

LOWEY:

Are there tremendous pressures on the FDA to keep it voluntary rather than mandatory? We had people who want to know. I can't understand why it can't be labeled accurately.

HAMBURG:

Well, I think there is a desire to operate within our legal regulatory framework in terms of when a mandatory label is appropriate versus a voluntary label and that's what -- but it's an area of, you know, ongoing discussion of course.

LOWEY:

Isn't problematic that many countries, Europe in particular, do require accurate labeling?

HAMBURG:

Well, you know, Europe has a very different attitude towards genetically-modified food.

(CROSSTALK)

LOWEY:

They want to know what they eat.

HAMBURG:

Their food safety agency, I think, has looked at the issue, and from a food safety point of view, you know, has issued reports that are more reflective of, you know, what I was saying earlier. But the European people have made a determination that they really don't want genetically-modified foods.

LOWEY:

Genetically-modified foods. Well, I won't pursue this today but it's beyond me that we can't have accurate labeling and I do hope that we can pursue this. The labeling can hurt anybody but it's possible that the lack of adequate labeling could. Thank you very much.

ADERHOLT:

Thank you, Ms. Lowey. Mr. Nunnelee?

Thank you. Thank you for being here today. Let me just in concluding cite the menu labeling issue as something is - you know, we're hearing a lot about so we would appreciate your concern and your focus on that and I know you will and just concerns that it cost (ph) a lot of businesses out there but regardless, thank you for being here today, for the last 2-1/2 hours and we appreciate all of your work here and all of you been here and the committee is adjourned.

HAMBURG:

Thank you.

CQ Transcriptions, March 27, 2014

List of Panel Members and Witnesses

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WITNESSES:

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NORRIS W. COCHRAN, DEPUTY ASSISTANT SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES

WILLIAM TOOTLE, DIRECTOR OF THE OFFICE OF BUDGET, FOOD AND DRUG ADMINISTRATION

AMA and AAAS Statements

H-480.958 Bioengineered (Genetically Engineered) Crops and Foods

Next Policy | Previous Policy

H-480.958 Bioengineered (Genetically Engineered) Crops and Foods

(1) Our AMA recognizes the continuing validity of the three major conclusions contained in the 1987 National Academy of Sciences white paper "Introduction of Recombinant DNA-Engineered Organisms into the Environment." [The three major conclusions are: (a)There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms; (b) The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; (c) Assessment of the risk of introducing rDNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.)

(2) That federal regulatory oversight of agricultural biotechnology should continue to be science-based and guided by the characteristics of the plant or animal, its intended use, and the environment into which it is to be introduced, not by the method used to produce it, in order to facilitate comprehensive, efficient regulatory review of new bioengineered crops and foods.

(3) Our AMA believes that as of June 2012, there is no scientific justification for special labeling of bioengineered foods, as a class, and that voluntary labeling is without value unless it is accompanied by focused consumer education.

(4) Our AMA supports mandatory pre-market systematic safety assessments of bioengineered foods and encourages: (a) development and validation of additional techniques for the detection and/or assessment of unintended effects; (b) continued use of methods to detect substantive changes in nutrient or toxicant levels in bioengineered foods as part of a substantial equivalence evaluation; (c) development and use of alternative transformation technologies to avoid utilization of antibiotic resistance markers that code for clinically relevant antibiotics, where feasible; and (d) that priority should be given to basic research in food allergenicity to support the development of improved methods for identifying potential allergens. The FDA is urged to remain alert to new data on the health consequences of bioengineered foods and update its regulatory policies accordingly.

(5) Our AMA supports continued research into the potential consequences to the environment of bioengineered crops including the: (a) assessment of the impacts of pest-protected crops on nontarget organisms compared to impacts of standard agricultural methods, through rigorous field evaluations; (b) assessment of gene flow and its potential consequences including key factors that regulate weed populations; rates at which pest resistance genes from the crop would be likely to spread among weed and wild populations; and the impact of novel resistance traits on weed abundance; (c) implementation of resistance management practices and continued monitoring of their effectiveness; (d) development of monitoring programs to assess ecological impacts of pest-protected crops that may not be apparent from the results of field tests; and (e) assessment of the agricultural impact of bioengineered foods, including the impact on farmers.

(6) Our AMA recognizes the many potential benefits offered by bioengineered crops and foods, does not support a moratorium on planting bioengineered crops, and encourages ongoing research developments in food biotechnology.

(7) Our AMA urges government, industry, consumer advocacy groups, and the scientific and medical communities to educate the public and improve the availability of unbiased information and research activities on bioengineered foods. (CSA Rep. 10, I-00; Modified: CSAPH Rep. 1, A-10; Modified: CASPH Rep. 2, A-12)

Statement by the AAAS Board of Directors On Labeling of Genetically Modified Foods

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

20 October 2012

There are several current efforts to require labeling of foods containing products derived from genetically modified crop plants, commonly known as GM crops or GMOs. These efforts are not driven by evidence that GM foods are actually dangerous. Indeed, the science is quite clear: crop improvement by the modern molecular techniques of biotechnology is safe. Rather, these initiatives are driven by a variety of factors, ranging from the persistent perception that such foods are somehow "unnatural" and potentially dangerous to the desire to gain competitive advantage by legislating attachment of a label meant to alarm. Another misconception used as a rationale for labeling is that GM crops are untested.

The EU, for example, has invested more than €300 million in research on the biosafety of GMOs. Its recent report[1] states: "The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than e.g. conventional plant breeding technologies." The World Health Organization, the American Medical Association, the U.S. National Academy of Sciences, the British Royal Society, and every other respected organization that has examined the evidence has come to the same conclusion: consuming foods containing ingredients derived from GM crops is no riskier than consuming the same foods containing ingredients from crop plants modified by conventional plant improvement techniques.

Civilization rests on people's ability to modify plants to make them more suitable as food, feed and fiber plants and all of these modifications are genetic. Twentieth century advances in the science of genetics opened the way to using chemicals and radiation as means of accelerating genetic change to produce nutritionally enhanced foods like lycopene-rich Rio Star grapefruit and quite literally thousands of other improved fruit, vegetable and grain crop varieties. Modern molecular genetics and the invention of large-scale DNA sequencing methods have fueled rapid advances in our knowledge of how genes work and what they do, permitting the development of new methods that allow the very precise addition of useful traits to crops, such as the ability to resist an insect pest or a viral disease, much as immunizations protect people from disease.

In order to receive regulatory approval in the United States, each new GM crop must be subjected to rigorous analysis and testing. It must be shown to be the same as the parent crop from which it was derived and if a new protein trait has been added, the protein must be shown to be neither toxic nor allergenic. As a result and contrary to popular misconceptions, GM crops are the most extensively tested crops ever added to our food supply. There are occasional claims that feeding GM foods to animals causes aberrations ranging from digestive disorders, to sterility, tumors and premature death. Although such claims are often sensationalized and receive a great deal of media attention, none have stood up to rigorous scientific scrutiny. Indeed, a recent review of a dozen well-designed long-term animal feeding studies comparing GM and non-GM potatoes, soy, rice, corn and triticale found that the GM and their non-GM counterparts are nutritionally equivalent[2].

It is the long-standing policy of the Food and Drug Administration (FDA) that special labeling of a food is required if the absence of the information provided poses a special health or environmental risk. The FDA does not require labeling of a food based on the specific genetic modification procedure used in the development of its input crops. Legally mandating such a label can only serve to mislead and falsely alarm consumers.

Approved by the AAAS Board of Directors on 20 October 2012

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1 http://ec.europa.eu/research/biosociety/pdf/ a_decade_of_eu-funded_gmo_research.pdf
2 Snell C, Bernheim A, Berge J-B, Kuntz M, Pascal G, Paris A and Ricroch A E (2012). Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: a literature review. Food and Chemical Toxicology, 50: 1134-48.