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Federal Regulation of Scientific Research

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August 2001 (revised in December 2001)

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This paper was prepared as part of the Advanced Methods of Cooperative Security Program at the Center for International and Secuirty Studies at Maryland, with generous support from the John D. and Catherine T. MacArthur Foundation.

Federal Regulation of Scientific Research: an initial overview

Summary
Three federal agencies share primary responsibility for regulating biotechnology: the Food and Drug Administration (FDA), the US Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), and the US Environmental Protection Agency (EPA). FDA is the lead regulatory agency for most foods, drugs, human biologics, and medical devices. General areas of responsibility:

Agency	Products Regulated
USDA	Plant pests, plants, veterinary biologics
EPA	Microbial/plant pesticides, new uses of existing pesticides, novel microorganisms
FDA	Food, feed, food additives, veterinary drugs, human drugs, and medical devices.

The following statutes apply only to specific types of products or activities and are administered by only one agency.[1]

- Animal and Plant Health Inspection Service (APHIS), in the USDA:
  - Animal Quarantine Laws (AQL), 21 USC 101-135
  - Plant Protection Act (PPA), 7 USC 7701-7772, which consolidated several previous statutes that APHIS used to regulate genetically engineered organisms, including the Federal Plant Pest Act (FPPA), 7 USC 150aa-150jj, the Plant Quarantine act (PQA), 7 USC 151-164a, 166-167, and others. Because no regulations have yet been issued pursuant to the PPA, APHIS continues to regulate biotechnology products according to the regulations issued regarding the FPPA, PQA, etc.
  - Virus, Serum Toxin Act (VSTA), 21 USC 151-159

- Environmental Protection Agency (EPA):
  - Federal Food, Drug, and Cosmetic Act (FFDCA), 21 USC 321, 246a et seq., as amended by the Food Quality Protection Act (FQPA), Pub. Law 104-170 (1996).
  - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 USC 136-136y, as amended by FQPA, supra.,
  - Toxic Substances Control Act (TSCA), 15 USC 2601-2692

- Food and Drug Administration (FDA), of the Department of Health and Human Services
  - FFDCA, 21 USC 321-397
  - Public Health Service Act (PHSA), 42 USC 262, 264

- Food Safety Inspection Service (FSIS), of the USDA
  - Federal Meat Inspection Act (FMIA), 21 USC 601-691
  - Poultry Products Inspection Act (PPIA), 21 USC 451-471
  - Egg Products Inspection Act (EPIA), 21 USC 1031-1056

[1] This compilation is taken from CEQ and OSTP Assessment: *Case Studies of Environmental Regulations for Biotechnology*. (Washington, DC: January 2001).

Background

Concerns about potential hazards of new techniques for transferring genes in the 1970s led to a call for a voluntary moratorium in 1974 on certain types of tests[2] and the Asilomar conference in February 1975. The consensus statement from the Asilomar conference recommended lifting the partial moratorium and replacing it with guidelines for genetic engineering research. The central assumption was that the unknown hazards of genetic engineering should be contained biologically and physically. This consensus formed the basis for the *NIH Guidelines* issued in 1976 upon advice from the recombinant DNA advisory committee (RAC).

Until 1984, the RAC was the primary federal entity that reviewed and monitored DNA research. However a legal challenge forced the Reagan Administration to consider and propose policies to guide activities of federal agencies responsible for reviewing biotechnology research and its products.[3] In 1986 the Office of Science and Technology Policy issued the Coordinated Framework for Regulation of Biotechnology.[4] It described the comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products. "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 Coordinated Framework established two principles: (1) 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. (2) To the extent possible, responsibility for a product use will lie with a single agency (or a lead agency or coordinated/consolidated reviews where more than one agency has jurisdiction). "Each regulatory review will require that the safety, or safety and efficacy, or a particular agricultural or industrial product be satisfactorily demonstrated to the regulatory agency prior to commercialization."

The two charts attached describe the regulations for the conduct of biotechnology research and the products of biotechnology. According to the Framework, "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. Jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products." (51 FR 23304).

A 1987 NAS white paper, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues* examined the safety of rDNA techniques and on ecological issues

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[2] "Potential Biohazards of Recombinant DNA Molecules," *Proceedings of the National Academy of Sciences*, USA v. 71, no. 7 (July 1974): 2593-2594.

[3] This observation is made in Donna U. Vogt and Mickey Parish, "Food Biotechnology in the United States: Science, Regulation, and Issues," *CRS Report to Congress* (June 2, 1999): 7. The legal challenge was *Foundation on Economic Trends v. Heckler*, 587 F. Supp 753 (D.C. 1984) 756 F.2d 143 (D.C. 1985).

[4] 51 FR 23302 (June 26, 1986). Notification was published at 49 FR 50856 (December 31, 1984).

associated with the potential spread of transgenic organisms or genes associated with transgenic organisms. Its findings supported the approach taken in the Coordinated Framework.

- Point 1 "There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms."
- Point 2 "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."
- Point 3 "Assessment of the risks 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.

A 2000 NAS report, *Genetically Modified Pest-Protected Plants: Science and Regulation*, found those principles to still be valid.

The remainder of this draft is organized by level of research. There are some overlapping areas of responsibility, most prominently for human gene therapy.

Basic Research (General)

- OSHA regulations require that agents are secured and handled consistent with the Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual. Lab directors are personally liable for not keeping a safe lab environment.[5] In 1986, OSHA found that its responsibilities under the Occupational Safety and Health Act of 1970 (29 USC 651 et seq.) provided an adequate and enforceable basis for protection of the safety and health of employees in the field of biotechnology. It stated that "the potentially hazardous character of some aspects of biotechnology is primarily from the chemicals used and not the biotechnology products…. No new regulations that specifically covered biohazards are warranted." (51 FR 23348)
- FDA reviews documents down to this level after an Investigational New Drug (IND) application is submitted as a precondition for beginning clinical trials. The review is post-hoc and designed to ensure that a drug/biologic was developed under the proper conditions to ensure its safety and efficacy. This applies to any drug/biologic going to market. Good Laboratory Practices (GLPs) must be observed at this phase if the drug or biologic is intended for market.

Basic Research (recombinant DNA)

- RAC review and NIH Director approval is required for the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture. (Major Actions). This is mandatory for institutions that receive any support for recombinant DNA research from NIH. (January 2001 *NIH Guidelines*.) Compliance by industry is voluntary. While there are incentives for industry to comply, it is uncertain to what degree they do.

[5] This liability is cited in Barry Kellman, "Biological Terrorism: Legal Measures for Preventing Catastrophe," *Harvard Journal of Law and Public Policy* v. 24, no.2 (Spring 2001): 450-451.

- Institutional Biosafety Committee (IBC) and NIH's Office of Biotechnology Affairs (OBA) approval is required before initiating experiments involving the cloning of toxin molecules with an LD_{50} of less than 100 nanograms per kilogram body weight (e.g. microbial toxins such as botulinum toxins, tetanus toxin, diphtheria toxin, etc). Approved experiments are listed in Appendix F. There are currently over 400 IBCs registered with NIH. Again, the *NIH Guidelines* are mandatory only for institutions receiving NIH funding for recombinant DNA work.. (January 2001 *NIH Guidelines*.)
- IBC approval of containment conditions is required for experiments that involve the introduction of recombinant DNA into restricted agents. NIH/OBA reviews these on a case by case basis and also reviews experiments in which DNA from restricted agents is transferred into nonpathogenic prokaryotes or lower eukaryotes.[6]

Preclinical Trials[7]

The Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 is the basic statute under which the federal government regulates foods, drugs, medical devices, and cosmetics. The 1962 Drug Amendments expanded FDA's authority, adding the requirement that a drug be effective in addition to safe to obtain premarket approval. Among other things, it mandates annual drug establishment registration; inspections of drug establishments every two years, and Good Manufacturing Practices (GMP) for all drugs. The 1997 Food and Drug Administration Modernization Act (FDAMA) was designed to expedite the premarket review process for new products.

A "new drug" is defined in section 201(p) of the FDCA as virtually any drug that first came on the market after the enactment of the 1938 Act unless the drug is "generally recognized as safe and effective." A new drug must have an approved NDA (or variant), to be marketed lawfully in the US.

There are six main routes to market for drugs/biologics:

1. New drug applications (NDAs)
2. Abbreviated new drug applications (ANDAs): This is for generic drugs. The ANDA applicant must pass all the same hurdles as for a full NDA, with one critical exception – the ANDA applicant need not demonstrate the safety and efficacy of its drug. It relies instead on the safety and efficacy of an already approved drug to which it must demonstrate its "bioequivalence."
3. Over-the-counter (OTC) review process
4. New animal drug applications (NADAs): the FDCA defines a "drug" as including articles "intended to affect the structure or function of the body of man or other animals" (21 USC § 321 (g)(1)(C). For example, a genetically engineered Atlantic salmon containing a fish growth hormone gene that is intended for commercial production requires a NADA. The process for obtaining a NADA tracks closely with that for a NDA.
5. Abbreviated new drug applications (ANADAs)

[6] The NIH Guidelines do not list the restricted agents. When OBA/NIH was contacted in July 2001, they could not state what a "restricted agent" was.

[7] Descriptions in the sections on preclinical and clinical trials are taken from Kenneth R. Pina and Wayne L. Pines, eds., *A Practical Guide to Food an d Drug Law and Regulation*. (Washington, D.C.: Food and Drug Law Institute, 1998).

The NDA is the standard model. The preclinical investigation is the first stage where the basic goals are to 1) identify the potential effects in the body of the chemical substance being investigated, through laboratory experimentation and animal testing; and 2) to gather enough evidence on the potential new drug to determine if it is reasonably safe to begin preliminary trials in humans.

Prior notification to FDA is not required to begin a preclinical investigation, although this phase is subject to specific FDA regulations known as Good Laboratory Practices (GLPs). These are codified in 21 CFR 58 and govern the lab work and facilities associated with any nonclinical study intended to support a marketing application for an FDA-regulated product. The regulations establish certain minimum requirements for different aspects of a testing lab's practices, subject the lab to FDA inspectional oversight, and provide penalties for noncompliance. For example, any study submitted to FDA in support of an application must be conducted with a detailed protocol specifying the study's objectives and methodologies, and that all relevant records and data from the study be retained for specific periods. Because failure to conform with applicable GLP requirements can result in the facility's being disqualified from carrying out any preclinical testing (and exclude a subsequent product application from consideration), the GLPs provide a strong incentive for sponsors who plan to take their product to market to take an active role in overseeing these studies.

Clinical Investigations

The primary goal of human clinical investigations is to gather sufficient information about the safety and efficacy of the drug to support an NDA. Commencement of clinical trials requires formal notification to FDA. At least 30 days before a sponsor wishes to begin such trials, the sponsor must submit an IND to the agency (21 CFR 312). If FDA does not object to the IND within 30 days, it automatically becomes effective and clinical trials may begin. FDA oversight is designed to protect both the health and safety of the human test subjects and ensure the integrity and usefulness of the study data.

The IND covers two basic categories of information: information on the study drug itself, and information on the proposed clinical investigation. It must include pharmacological and toxicological data. Further, it must contain a commitment from the sponsor to conduct clinical trials under the supervision of an Institutional Review Board (IRB) and follow all applicable rules and regulations. The Office of Human Research Protection (OHRP) oversees the work of the IRBs. All research that is conducted, supported, or regulated by any US Government Agency under the Federal Policy for the Protection of Human Subjects is subject to certain uniform requirements regarding IRB membership, IRB review and approval criteria, IRB operations and recordkeeping, and informed consent.

- IRBs (21 CFR 50 and 56). The fundamental goal of the regulatory requirements for informed consent and review of clinical studies by IRBs is to ensure the protection of the rights and welfare of human subjects. The IRB is essentially a committee designated by an institution to review biomedical research involving human subjects. IRB approval is required before a clinical study can begin and must continue to monitor the research. IRB members must come from diverse disciplines to review not only the specific research issues,

but also the study's acceptability under community and legal standards, as well as professional conduct and practice norms. The IRB must keep detailed records which are subject to FDA inspection. IRBs typically have 15 to 21 members on average, but unaffiliated members do not have to be present for an IRB to conduct review and approve research studies.[8] The central ethical and procedural function of IRBs is the determine whether a study poses more than minimal risk to the participants. However, there is no clear criteria for IRBs to use in judging whether the risks of research are reasonable in terms of what might be gained by the individual or society.

After phase 3 clinical trials are complete, the applicant can submit an NDA (requirements codified at 21 CFR 314). Specific NDA requirements are lengthy and detailed and include:

1. pre-clinical data;
2. human pharmacokinetic and bioavailability data;
3. clinical data demonstrating that the drug is safe and effective under the proposed conditions of use;
4. a description of the proposed methods by which the drug will be manufactured, processed, and packed;
5. a description of the drug product and drug substance;
6. a list of each patent claiming the drug, drug, product, or method or use, or a statement that there are no relevant patents making such claims;
7. the drug's proposed labeling; and
8. summary of the risks and benefits of the new drug.

Unless an application is publicly disclosed or acknowledged, FDA will keep the application a secret until the agency sends an approval letter. The contents remain secret even if the existence of an application is known.

FDA approval is dependent on whether it finds the drug safe and effective. The FDA weighs the product's demonstrated effectiveness against its risks to determine whether the benefits outweigh the risks. There must also be adquate manufacturing controls in place before the FDA will approve a drug. Good Manufacturing Practices (GMPs) must be adequate to ensure the drug's purity, quality, strength, identity, and bioavailability. A preapproval inspection of the applicant's facility is typically conducted to verify compliance with GMPs.

Human gene therapy

Human gene therapy is a special case that involves review by both the FDA and NIH/RAC prior to initiation. As discussed above, IRB and IBC approval is also required prior to initiation of human gene therapy trials. While this is mandatory for those institutions that fall under the NIH Guidelines, industry often complies voluntarily to shield themselves in the event that something untoward happens in the course of the clinical trial. In HHS, the Office of Human Research Protection (OHRP) oversees the work of IRBs.

Adverse event reporting is also shared by both organizations. It seems from RAC meeting notes that the FDA and RAC are trying to harmonize their efforts and streamline the process for review

[8] National Bioethics Advisory Committee Report, "Ethical and Policy Issues in Research Involving Human Participants, volume I," Bethesda, MD (August 2001): xv.

of gene therapy protocols and for adverse event reporting. However, FDA clearly has more authority over such experiments.[9]

An important difference between the FDA and NIH is in the protection of CPI. Information submitted to FDA for review is held as confidential. At the RAC/NIH, the information is assumed to be public unless explicitly marked confidential. The precedent at RAC is for open public discussion of all materials and seems to be quite explicit and detailed. Because industry may be more interested in such trials, CPI concerns may mean that RAC's authority is diminished further.

Human Biologics

Biological products -- biologics -- are medical products derived from living organisms. They are regulated under section 351 of the Public Health Service Act (PHSA) (42 USC § 262) and under various provisions of the FDCA. It is defined in the PHSA as, "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivatives of arsphenamine applicable to the prevention, treatment, or cure of a disease or condition of human beings." Marketing in interstate commerce requires a biologics license issued by FDA on the basis of a demonstration that the product is safe, pure, and potent (as is the manufacturing conditions). The Center for Biologics Evaluation and Research (CBER) at FDA regulates biological products.

Originally, biologics were subject to a bifurcated system under which a manufacturer had to obtain a product license by means of a product license application (PLA), and the establishment where the product was manufactured had to obtain an establishment license through an establishment license application (ELA). In May 1996 this was eliminated for certain categories of biologics and replaced by the biologics license application (BLA) with a detailed section on chemistry, manufacturing, and controls that effectively replaced the ELA. Now the approval process for biologics is similar to that described above for new drugs.

Animal Biologics

Biological products – products produced from living beings, such as sera, antitoxins and the like – intended for therapeutic use in animals are subject to the 1913 Virus-Serum-Toxin Act (VST Act). Animal biologics, however, unlike human biologics are regulated by the USDA. The VST Act made it illegal to ship from one state to another any virus, serum toxin, or analogous product intended for use in the treatment of domestic animals unless the product was prepared in accordance with regulations issued by USDA at an establishment holding a current license from USDA (21 USC § 151). USDA has a system of licensing animal biologics and the establishments that produce them whose main substantive features parallel those of the FDA animal drug regulation (9 CFR subch. E).

The Animal and Plant Health Inspection Service (APHIS) at USDA is responsible for protecting US agriculture from pests and diseases. Under the authority of the Federal Plant Pest Act, APHIS regulations provide procedures for obtaining a permit or for providing notification, prior to "introducing" a regulated article in the United States. Regulated articles are considered to be

[9] See the minutes of the March 8, 2001 meeting of the Recombinant DNA Advisory Committee. Downloaded from http://www4.od.nih.gov/oba/rac/meeting.html.

organisms and products altered or produced through genetic engineering that are plant pests or that there is reason to believe are plant pests. The act of introducing includes any movement into (import) or through (interstate) the United States, or release into the environment outside an area of physical confinement. It also describes a for a petition process for the determination of nonregulated status.

A plant pest is a risk to other plants and ecosystems. The term is generally applied to weeds, insects, diseases, or untested genetically modified organisms (GMOs).

A company, academic research institution, or public sector scientist wishing to move or field-test a genetically engineered plant must obtain the necessary permit(s) before proceeding. To move any genetically engineered organism that is a potential plant pest into the United States or between states, permit applicants must provide APHIS with details about the nature of the organism, its origin, and intended use. The appropriate state department of agriculture reviews the application after APHIS.

Environmental release

The EPA ensures the safety of pesticides, both chemical and those that are produced biologically. The BioPesticides and Pollution Prevention Division of the Office of Pesticide Programs (OPP) under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 USC 136) to regulate the distribution, sale, use and testing of plants and microbes producing pesticidal substances.

The Toxic Substances Control Act (TSCA) (15 USC 53), EPA's TSCA Biotechnology Program regulates microorganisms intended for commercial use that contain or express new combinations of traits. This includes "intergeneric microorganisms" formed by deliberate combinations of genetic material from different taxonomic genera.

APHIS (USDA) also oversees field testing (environmental release) of genetically engineered crops. An applicant must provide complete information about the plant, including all new genes and new gene products, their origin, the purpose of the test, the experimental design and precautions to prevent the escape of pollen, plants, or plant parts from the field test site.

APHIS also prepares Environmental Assessments (EA). Under the National Environmental Policy Act (NEPA) (42 USC 4332), federal agencies must consider environmental impacts of proposed major federal actions that could significantly affect the environment. If an EA indicates that the proposed action could significantly affect the environment, the agency must prepare a more comprehensive "Environmental Impact Statement" which includes an examination of project alternatives.

Inspections

<u>FDA</u>

FDA's Bioresearch Monitoring Program (BIMO) is a comprehensive program of on-site inspections and data audits designed to monitor all aspect of the conduct and reporting of FDA regulated research. The program is implemented domestically and internationally through four

multi-center compliance programs resulting in over 1000 inspections annually.[10] These compliance programs address inspections of nonclinical testing labs (GLP), clinical investigators (GCP), sponsors/monitors and institutional review boards (IRB).

ASM estimates that FDA is only able to inspect 28% of drug manufacturer facilities annually. (May 2001 report)

EPA

EPA is responsible for setting tolerances for pesticide residues in or on raw agricultural commodities and processed foods under the FDCA (21 USC 346 and 348) and for registering pesticides under FIFRA (7 USC 136). Also, under the TSCA, the EPA is mandated to assure that no chemical will present an unreasonable risk of injury to health or the environment. EPA regulatory decisions on such matters are based in part on the results of toxicological testing performed by or for registration applicants, tolerance petitioners, and chemical manufacturers. Therefore it is essential that such testing provide an objective and reliable basis for decision-making.

Under an interagency agreement with FDA, FDA audits selected health-related toxicological test reports and related lab records in order for EPA to determine (1) whether the testing was performed in accordance with the test protocols; (2) whether any reported deviations may have affected the reliability of the test results; (3) whether the test reports fully and accurately reflected the test procedures and results.

Transfer of Select Agents

Centers for Disease Control and Prevention (CDC)

The CDC program for Select Agent transfers is designed to (1) ensure that the listed infectious agents and toxins are shipped only to institutions or individuals equipped to handle them appropriately; (2) transfer of these agents is to those who have legitimate reasons to use them, and (3) a system is implemented whereby scientists and researchers involved in legitimate research may continue transferring these agents without undue burdens. (42 CFR 72)

Approximately 40 viruses, bacteria, rickettsia, fungi, and toxins are on the list. Prior to transfer, both the shipper and receiver must be registered with the LR/SAT Program (CDC) or meet requirements for exemption. Upon termination of use, the agent must be transferred to another registered facility or destroyed on site (and reported to the CDC).

As of October 2000, 200 facilities have registered (42% academic, 21% commercial, 20% governmental, and 17% private sector).[11] The majority of facilities are at BL-2 because work with genetic sequences are covered. (The rules are, I understand, changing a bit and may or may not cover all genetic sequences of select agents in the future.) According to the rules, each facility is visited at least once in a three-year registration period.

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[10] This description and this 1998 figure is from the Office of Regulatory Affairs (ORA) at FDA. Downloaded from www.fda.gov/ora/compliance_ref/bimo/background.html on 4/18/01.

[11] This information was obtained from Mark Hemphill, CDC in a phone conversation in October 2000.

Bureau of Export Administration (BXA)

The International Emergency Economic Powers Act and the Export Administration Act of 1979 provide the BXA with the authority to regulate the export and re-export of dual-use commodities and technologies on the US Department of Commerce Control List (CCL) of the Export Administration Regulations. BXA coordinates the licensing process for the Australia Group-controlled biological, equipment for handling biological materials, and the technology for their development, production, and use. The process includes a review by DoD, State, and CIA. Less than two percent of total US exports require licenses from BXA. In 2000, BXA approved 430 applications for the export of items and technologies controlled for biological weapons concerns. BXA denied only one export of a biological item in 2000.[12]

[12] The information on BXA is taken from a statement made by Douglas Brown, BXA at a conference in Stockholm, Sweden in June 2001.

Chart 1: Coordinated Framework -- Approval of Commercial Biotechnology Products

Subject	Responsible agency (agencies)
Foods/Food Additives	FDA,* FSIS[1]
Human Drugs, Medical Devices and Biologics	FDA
Animal Drugs	FDA
Animal Biologics	APHIS
Other Contained Uses	EPA
Plants and Animals	APHIS*, FSIS, FDA[2]
Pesticide Microorganisms Released in the Environment All.	APHIS[3]
Other Uses (Microorganisms):	
Intergeneric Combinations	EPA*, APHIS[3]
Intrageneric 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-agricultural Use	EPA*[4], APHIS[3]
Nonengineered Nonpathogens	EPA report

This is from the "Coordinated Framework for Regulation of Biotechnology 51 FR 23302 (6/26/86)
* Lead Agency

[1] FSIS, Food Safety and 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 food use

[3] APHIS, Animal and Plant Health Inspection Service, is involved when the microorganism is a plant pest, animal pathogen, or regulated article requiring a permit.

[4] EPA requirements will only apply to environmental release under a "significant new use rule" (TBA).

Narrative description:

Jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products.

Food, 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 FSIS jurisdiction.

Animal biologics are reviewed by APHIS. APHIS also reviews plants, seeds, animal biologics, plant pests, animal pathogens and "regulated articles" (i.e. 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 to TSCA that are intergeneric combinations (microorganisms which contain genetic material from dissimilar source organisms). These are subject to EPA's PMN 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.)

"Intrageneric combinations" are those microorganisms formed by genetic engineering other than intergeneric combinations. For these, when there is a pathogenic source organism and the organism 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 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.

Chart 2: Coordinated Framework -- Biotechnology Research Jurisdiction

Subject	Responsible agency(agencies)
Contained Research, no release in environment	
1. Federally Funded	Funding agency[1]
2. Non-Federally Funded	NIH or S&E voluntary review
Foods/Food Additives, Human Drugs, Medical Devices, Biologics, Animal Drugs:	
1. Federally Funded	FDA*, NIH Guidelines & review
2. Non-Federally Funded	FDA*, NIH voluntary review
Plants, Animals, and Animal Biologics:	
1. Federally Funded	Funding agency[1], APHIS[2]
2. Non-Federally Funded	APHIS*, S&E voluntary review
Pesticide Microorganisms:	
Genetically Engineered	
Intergeneric	EPA*, APHIS[2], S&E voluntary review
Pathogenic Intergeneric	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 (Microorganisms) Released in the Environment	
Genetically Engineered	
Intergeneric Organisms	
1. Federally Funded	Funding agency[1], APHIS[2], EPA[4]
2. Commercially Funded	EPA, APHIS, S&E voluntary review
Intrageneric Organisms	
Pathogenic Source Organism:	
1. Federally Funded	Funding agency[1], APHIS[2], EPA[4]
2. Commercially Funded	APHIS[2], EPA (if non-agricultural use)
No Pathogenic Source Organism	EPA Report
Nonengineered	EPA Report*, APHIS[2]

This is from the "Coordinated Framework for Regulation of Biotechnology 51 FR 23302 (6/26/86)

* Lead Agency. 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). The authority refers to approval of the actual execution of experiments and not to their funding.

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

[2]APHIS issues permits for the importation and domestic shipment of certain plants and animals, 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.

Narrative description

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.

Fasioned 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, or 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 microoganisms with lesser notification required for level I reporting and full review for level II.

For the "other uses" category, 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.