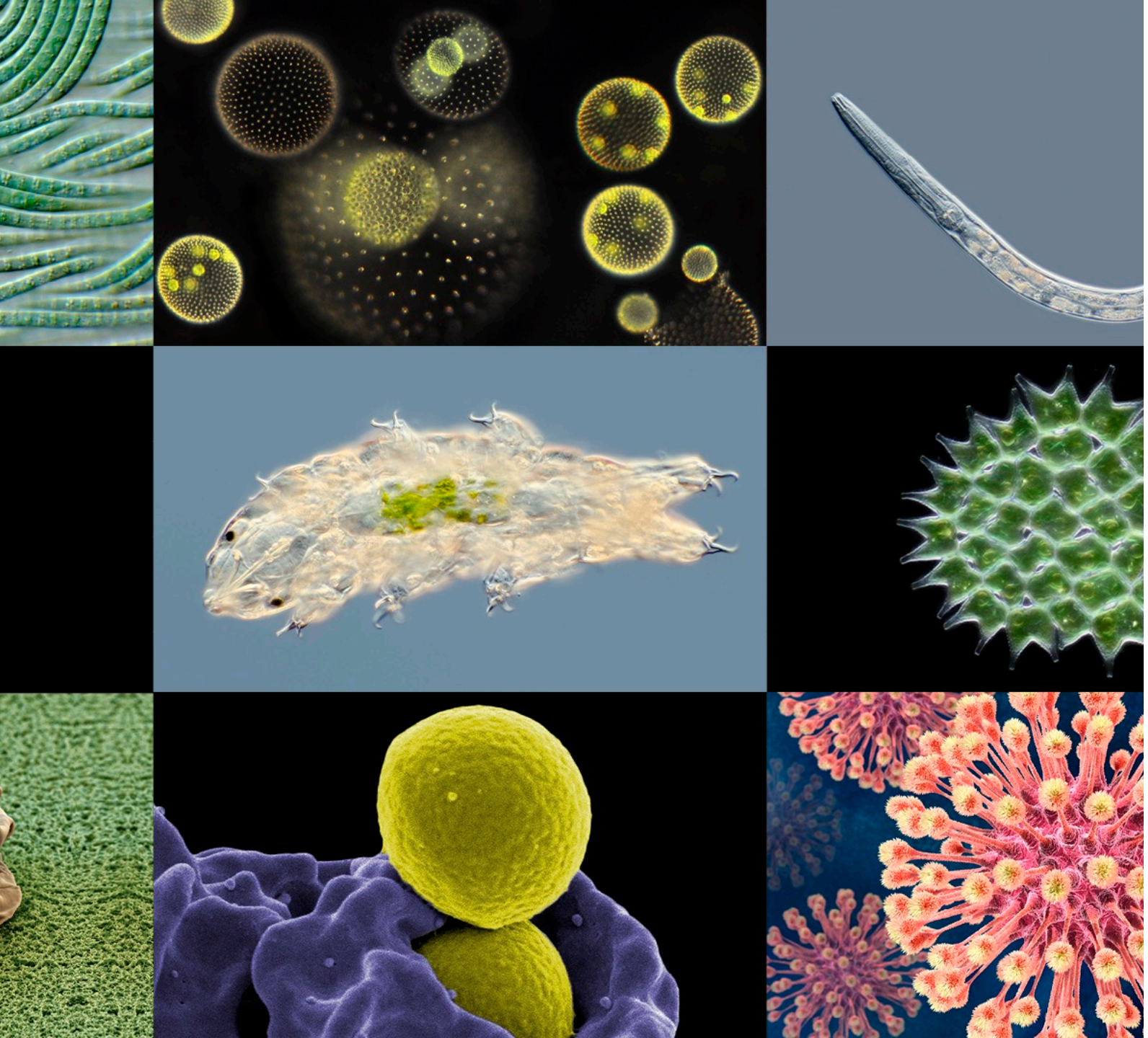
Regulation of Genetically Engineered Microbial Pesticides at EPA

Kara Welch, welch.kara@epa.gov
Emerging Technologies Branch
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency



Agenda

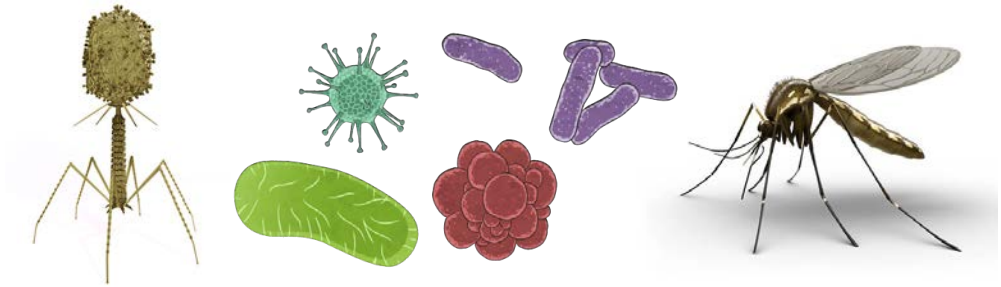
- What is a pesticidal active ingredient?
- What statutes does OPP oversee?
- Types of Regulatory Pathways
- Data Requirements
- Best Practices

What is a pesticidal active ingredient?

- Active ingredient means any substance (or group of structurally similar substances, if specified by the Agency) that will ***prevent, destroy, repel or mitigate any pest***, or that functions as a plant regulator, desiccant, defoliant, or nitrogen stabilizer (FIFRA)
- EPA oversees microbial pesticides, both GE and non-GE. There are field testing requirements for GE microbes

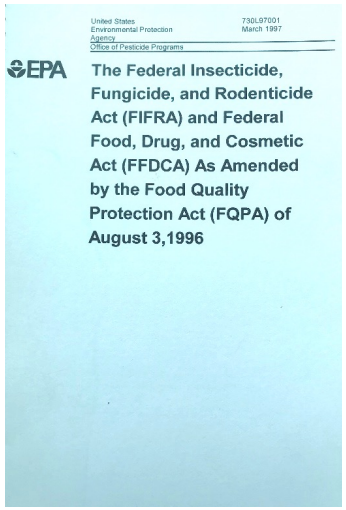
Types of Microbial Active Ingredients

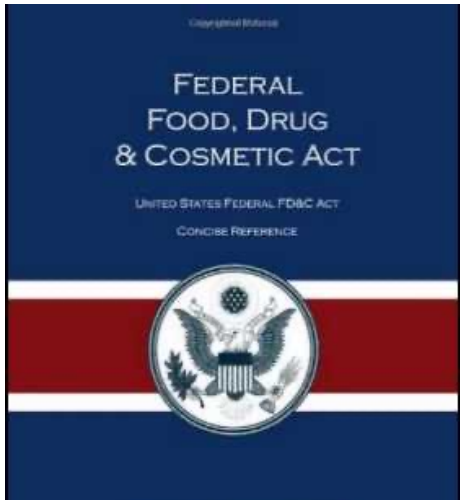
- Bacteriophage
- Viruses (e.g., baculoviruses, plant virus)
- Bacteria
- Fungi
- Algae
- Protozoa
- Paratransgenic insect symbionts such as *Wolbachia* in mosquitoes

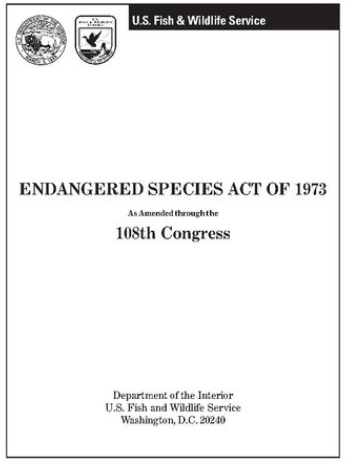


EPA's Regulatory Role

- **Federal Insecticide, Fungicide and Rodenticide Act** (FIFRA) - pesticides
  - No unreasonable adverse effects upon human health and the environment
- **Federal Food Drug and Cosmetic Act** (FFDCA) - food and feed safety
  - Reasonable certainty of no harm from aggregate exposure to a pesticide chemical residue
- **Pesticide Registration Improvement Act** (PRIA)
  - Pesticide registration fee-for-services and EPA decision timelines
- **Endangered Species Act**



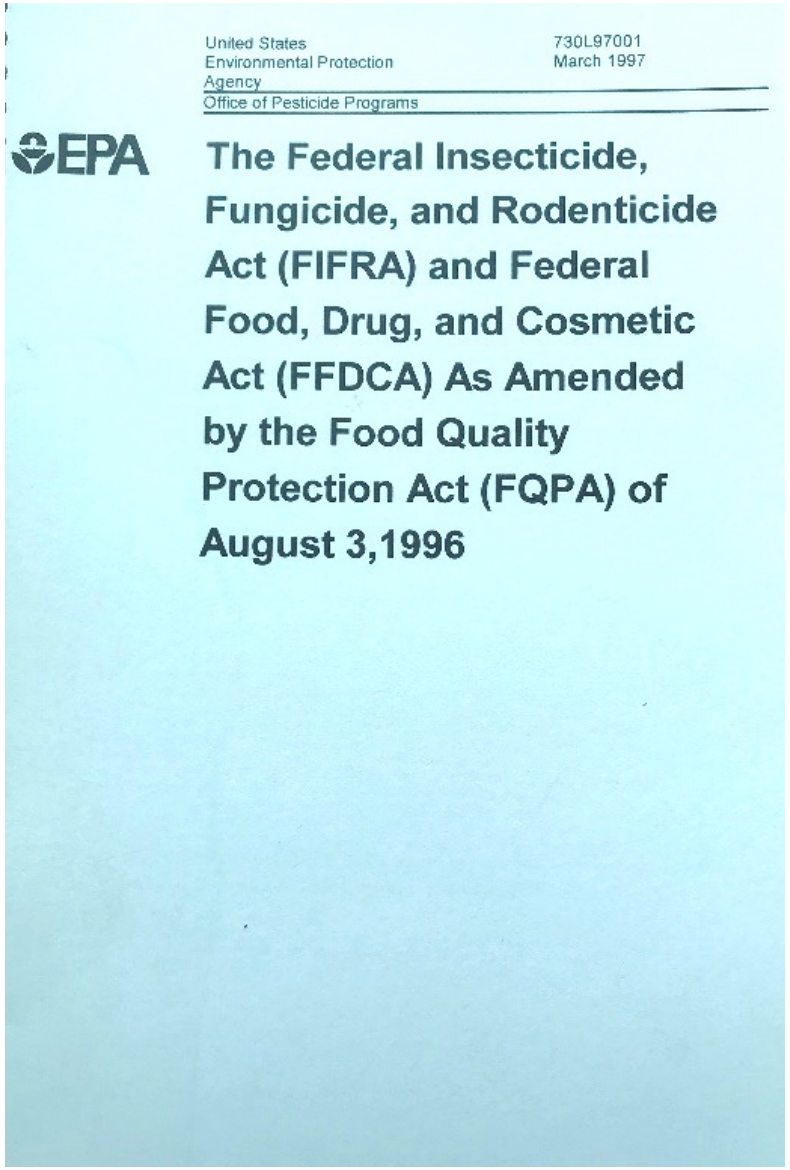




Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Actions

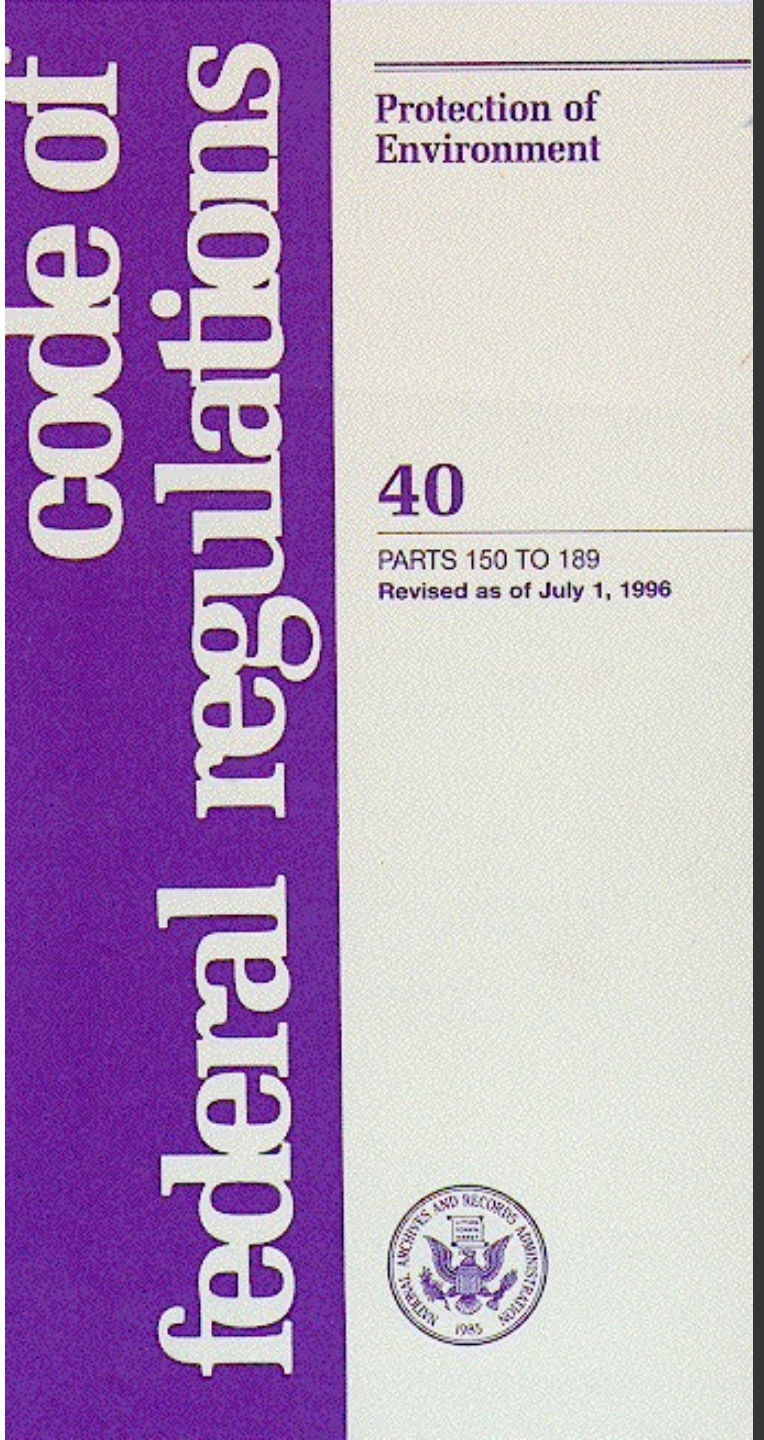
- Notifications for small scale field testing*
  - Genetically engineered and non-indigenous microbial pesticides, <10 acres
- Experimental Use Permits (Sec. 5)
  - Field testing on more than 10 acres of land, 1 acre of water
- Special Local Needs (Sec. 24c) and Emergency Exemptions (Sec. 18)
- Pesticide registration (Sec. 3)
  - Commercial use
- Registration review (Sec. 3(g))
  - Pesticides reassessed every 15 years

*Biotechnology notifications are a unique registration step for GE products



158 Data Requirements

- The Code of Federal Regulations (CFR) is the 'play book' to FIFRA's statutory authority
- Part 158 Subpart V describes the nature of microbial pesticides and data requirements for registration
  - https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158/subpart-V
- Primarily, genetically modified microbial pesticides require additional product characterization data



Unique field-testing requirements

- Unlike other pesticides which require experimental use permits if field testing occurs over more than 10-acres, notification is required for small scale testing for products of biotechnology
- Unique data requirements for biotechnology notifications are in Part 172 Subpart C § 172.48
  - https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-172/subpart-C/section-172.48

(a) The identity of the microorganism which constitutes the microbial pesticide including:

(1) Summary of data supporting the taxonomic designation and its interpretation.

(2) Means and limit of detection using sensitive and specific methods (e.g., note the use of any markers that are used to distinguish the introduced population from native microorganisms). Introduction into the microbial pesticide of a unique genetic marker is encouraged.

(b) Description of the natural habitat of the parental strain of the microbial pesticide including information on:

(1) Physical and chemical features important to growth and survival of the parental strain.

(2) Biological features of the parental strain that would have an impact on the microbial pesticide (e.g., presence of phages that infect the microorganism).

(3) Competitors.

(c) Information on the host range of the microbial pesticide, if any, with an assessment of infectivity and pathogenicity to nontarget organisms.

(d) Information on survival and the ability of the microbial pesticide to increase in numbers (biomass) in the environment (e.g., in the environment into which the microbial pesticide will be introduced, and in substantially different environments that may be in the immediate vicinity). These data may be derived from the scientific literature or from tests conducted in a laboratory or other containment facility.

(e) The identity of possible transmission vectors (e.g., insects).

(f) Data on relative environmental competitiveness compared to the parental strain of the microbial pesticide.

(g) Description of the methods used to genetically modify the microbial pesticide.

(h) The identity and location of the gene segments that have been rearranged or inserted/deleted (host source, nature, and, for example, base sequence data, or restriction enzyme map of the genes).

(i) Information on the control region of the genes, and a description of the new traits or characteristics that are expressed.

(j) Data on potential for genetic transfer and exchange with other organisms and on genetic stability of any inserted sequences in the microbial pesticide.

(k) A description of the proposed testing program including:

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

(2) Designation of the pest organisms involved (common and scientific names).

(3) The States in which the proposed program will be conducted.

(4) The exact location of the test sites (including proximity to residences and human activities, surface water, etc.).

- Be aware that notifications should be submitted for approval at least 90 days prior to the initiation of the proposed testing

Unique field-testing requirements

(5) 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.

(6) The total amount of pesticide product proposed for use in the testing.

(7) The method of application.

(8) A comparison of the natural habitat of the microbial pesticide with the proposed test site.

(9) The number of acres, structural sites, or animals/plants by State, to be treated or included in the area of experimental use.

(10) Procedures to be used to protect the test area from intrusion by unauthorized individuals.

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

(12) Description of procedures for monitoring the microbial pesticide within and adjacent to the test site during the test.

(13) The method of sanitation or disposal of plants, animals, soils, farm tools, machinery etc., that will be exposed to the microbial pesticide during or after the test.

(14) Means of evaluating potential adverse effects and methods of controlling the microbial pesticide if detected beyond the test area.

(l) A statement of composition for the formulation to be tested, giving:

(1) The name and percentage by weight (or other suitable units) of each ingredient, active and inert.

(2) Production methods.

(3) Extraneous microorganisms present as contaminants.

(4) Amount and potency of any toxin present.

(5) 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.

(m) Any additional factual information regarding the potential for unreasonable adverse effects on the environment.

Series 885 – Microbial Pesticide Test Guideline Series

- Generally, the same data needs apply for GE or non-GE microbial pesticides with exceptions described in CFR Part 158 Subpart V
  - Some additional data may be requested on a case-by-case basis

- **Product Analysis**
  - Requires information on taxonomy, natural history, target, and non-target host range
    - *For GE microbes*: Transformation event, sequence of transgene, restriction map, DNA source info, transgene stability

- **Human Health**
  - Introduces the AI via oral, pulmonary, and injection routes into animal surrogates

- **Environmental Effects**
  - Pathogenicity of related species and unrelated (wild mammals, birds, fish, beneficial insects, aquatic inverts, estuarine/marine, plants, honeybee) as well as environmental fate
  - Applicants may request a waiver from data requirements or bridge from one dataset to another

- Efficacy*
  - Only for public health pesticides (e.g., active against mosquitoes, termites, roaches, etc.)

Series 885 – Microbial Pesticide Test Guidelines

The final Microbial Pesticide Test Guidelines are generally intended to meet testing requirements for chemical composition, environmental impacts and human health effects to support the registration of microbial pest control agents under FIFRA.

885.0001 - Overview for Microbial Pest Control Agents (February 1996)

Group A – Product Analysis Test Guidelines

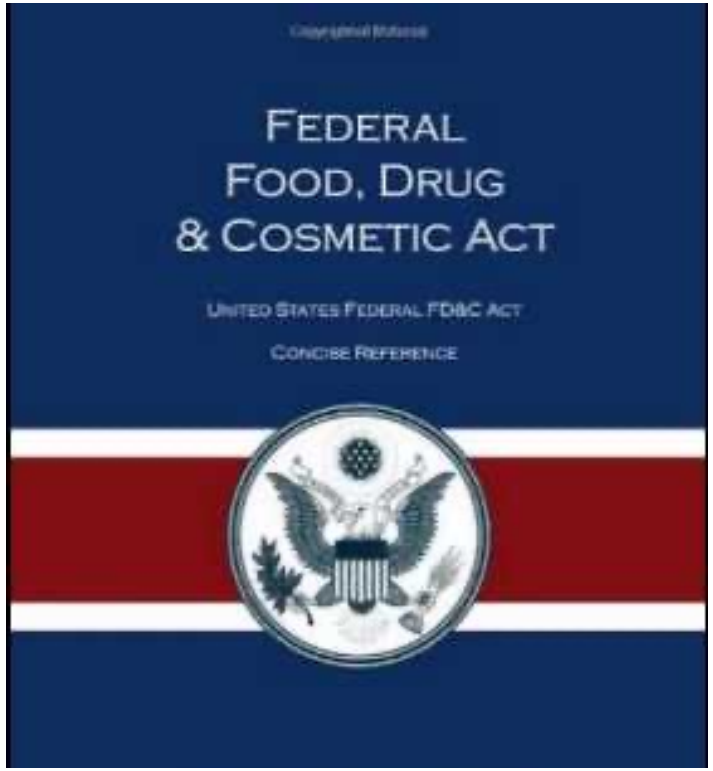
885.1100 - Product Identity (February 1996)
885.1200 - Manufacturing Process (February 1996)
885.1250 - Deposition of a Sample in a Nationally Recognized Culture Collection (April 2012)
885.1300 - Discussion of Formation of Unintentional Ingredients (February 1996)
885.1400 - Analysis of Samples (February 1996)
885.1500 - Certification of Limits (February 1996)

Group B – Residues Test Guidelines

885.2000 - Background for Residue Analysis of Microbial Pest Control Agents (February 1996)
885.2100 - Chemical Identity (February 1996)
885.2200 - Nature of the Residue in Plants (February 1996)

Federal **F**ood, **D**rug, and **C**osmetic **A**ct (FFDCA) Actions

- Tolerances and/or tolerance exemptions
  - Food and feed uses
  - Issued as rules – published in 40 CFR 180



Pesticide Registration Improvement Act (PRIA) Timelines

EPA Code	Action	Decision Timeline	FY 22'-23' Fees
B590	New AI, tolerance exemption	18 months	$35,182
B600	New AI, non-food use	13 months	$21,110
B610	New AI, Experimental Use Permit, with temporary tolerance or an exemption	10 months	$14,074

Biotechnology notifications are not a PRIA action and must be submitted at least 90 days prior to field testing

What does a pesticide application look like?

- Service fee(s) required by the Pesticide Registration Improvement Act (PRIA)
- Forms describing the requested action
- **The identity and quantity of all chemicals in the product**
- **Data on potential risks to human health and the environment, including about the potential for pesticide residues on food (if applicable)**
- **Proof that the product manufacturing process is reliable**
- Labeling, including directions for use, contents, and appropriate warnings

Best Practices for Registration Applications

- EPA encourages **pre-submission meetings** with the Emerging Technologies Branch to discuss product concepts and data submission strategies
- Note, all small-scale field testing of pesticide products of biotechnology must be submitted to EPA as a biotechnology notification
- Submit a description of the manufacturing process for creating the end-use product that can be easily understood by the EPA reviewer as if they were an outside party following the protocol
- Fully describe how the data submitted meet the data requirements. In addition to data submitted consider including information about the lack of hazard and the lack of exposure. Cite references if possible
- If submitting literature to address a data requirement, fully describe how the publication being submitted satisfies data requirements.
- If submitting data waiver request, explain why that data requirement is inappropriate, why it is not possible to generate the data, or why the data would not be useful for the Agency's assessment.
- If 100% technical grade active ingredient (TGAI) could not used in testing, provide justification as to why
- Discuss the dose selection and its relationship to the expected environmental concentration

Regulatory Guidance

- EPA Book Chapter on GE microbe regulation, https://www.epa.gov/sites/default/files/2015-09/documents/ch4-wozniak-etal-fifra-ffdca-tsca-112012_0.pdf
- Pesticide Registration Process, https://www.epa.gov/pesticide-registration/about-pesticide-registration
- Microbial Pesticide Registration, CFR Part 158 Subpart V https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158/subpart-V
- Biotechnology Notification Guidance CFR 40 § 172.48 https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-172/subpart-C/section-172.48
- Microbial Risk Assessment 885 Guidelines, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-885-microbial-pesticide-test-guidelines
- Guidance for Bridging or Waiving Data Requirements, https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements