

A Decision Support Tool for Determining Federal Regulatory Authority over Products for Vertebrate Animals

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ABSTRACT: Products developed for vertebrate animals, including toxicants, repellents, contraceptives, vaccines, drugs, antimicrobials, diagnostic kits, and some devices, are regulated under a suite of federal laws. Authorization for the production, sale, and use of these products is primarily controlled by three federal agencies: the U.S. Environmental Protection Agency's (EPA) Office of Pesticide Programs, the U.S. Food and Drug Administration's (FDA) Center for Veterinary Medicine, and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). Furthermore, regulatory oversight of these products extends to research activities conducted during their development. However, determining the regulatory jurisdiction of new products can be confusing for researchers and product developers. In fact, the same product could be regulated under different laws and by more than one agency depending on its intended target population, function, product claims, and route of administration. Adding to this complexity, EPA, FDA, and APHIS have reached a series of formal and informal agreements on which agency will have primary oversight for a number of novel product types that do not clearly fall into established product categories. Here, we present a decision support tool that helps researchers and product developers identify the regulatory jurisdiction of new products, allowing them to comply with federal laws and consult with the appropriate agency early in the research and development phase. Such consultations ensure that resources are spent on studies that satisfy agency-specific data requirements for product registration, approval, and licensing.

KEY WORDS: animal drug, approval, device, licensing, pest, pesticide, product, registration, regulation, veterinary biologic

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INTRODUCTION

Most products designed to affect vertebrate animals are considered regulated articles under U.S. federal law unless they have been specifically exempted. Regulated articles must be reviewed and authorized by the federal agency that holds regulatory authority before they can be legally produced, marketed, distributed, sold, or used or released into the field. Here, we present a decision support tool to help researchers and product developers identify the primary federal regulatory agency that will likely have jurisdiction over the federal authorization of their product. The group of federally regulated articles covered by this decision tool are those substances, organisms, molecules, instruments, or other contrivances that are designed, manipulated, or modified, and used to directly affect the structure or function of the body of a non-human vertebrate animal for a specific purpose, or to control or prevent a parasite or disease-causing organism of a vertebrate animal. They include, but are not limited to, products that function as toxicants, repellents, sterilants, genetically-engineered organisms or their by-products, immunomodulators, hormone therapies, medicines, antiseptics, antimicrobials, antiserums, antitoxins, and diagnostic kits, and certain instruments and mechanical devices.

Firearms or other weapons triggered, held, or directly operated by a human at the time they are used on a vertebrate animal are also regulated but do not fall within the scope of this paper. Biological control animals, plants, or microorganisms that are not genetically modified and products that indirectly affect vertebrate animals by destroying their habitat are also federally regulated but are not discussed in this paper.

How a product is classified for regulatory purposes is determined by multiple factors, including its intended use or affect, mechanism of action, potential or known hazards, and the characteristics of the individual vertebrate animals or disease organisms on or against which it will be used. For example, when used on individuals of the same species, but in different contexts and for different goals, the same product could potentially be legally classified as either a new animal drug, a veterinary biological product, or a pesticide, which are each regulated by different agencies under different regulatory laws and requirements. This regulatory scene has only become more complicated as novel product types emerge and the uses of existing product types diverge from conventional methodologies. Thus, it is sometimes challenging for researchers and product developers to determine how their potential products will be regulated. Yet, early knowledge of a potential product's regulatory jurisdiction is crucial for researchers and product developers, because these products are usually subject to federal regulatory requirements even during the research and development phase, and not just after federal authorization has been obtained for production, distribution, sale, and use. Authorization is often required prior to using experimental products in animals. Depending on the regulatory agency, some form of notification or authorization is also required prior to importing, exporting, or inter-state transport of research products and their components even when they are to be used in confined laboratory or field trials. Use of a regulated research substance in an unconfined field setting is usually permitted only after the regulatory agency has received specific data and has approved research protocols for the product. Determining the regulatory requirements early will help developers avoid violating federal regulations and focus their research efforts, which expedites the authorization process. In general, data generated to support product authorization must follow specific guidelines and standards developed by the regulatory agency. Federal regulatory agencies encourage product developers to consult with them early in order to confirm the regulatory jurisdiction of their product, and to ensure compliance with the appropriate federal law(s).

CLASSIFICATIONS OF FEDERALLY-REGULATED PRODUCTS

New Animal Drugs and Veterinary Devices

All substances (including organisms or products derived from their components) that are “intended to affect the structure or any function of the body” of an animal in a manner other than food (nutrition, aroma, or taste) or “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals,” and any articles intended to be a component of these products, are classified as *drugs* under the Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. § 321(g)). Drugs for animals other than humans fall under the new animal drug provisions of FFDCA and must be approved or otherwise authorized by the U.S. Food and Drug Administration's Center for Veterinary Medicine (FDA CVM). In addition, drugs that are distributed in or on food (i.e., medicated feeds) must be

approved or otherwise authorized as used in such animal feed, and the medicated feed must be manufactured at a licensed facility (21 U.S.C. § 360b(a)(2)). Animal food/feed and dietary supplements for animals are themselves classified as drugs when the expressed or implied claims for the product suggest that the product falls under FFDCA's definition of a drug, although whether the product is regulated as a drug or as an animal feed depends on how it claims to change the structure or function of the body of an animal (FDA CVM 1998). All other supplements or substances intentionally added to animal feed are regulated as *food additives* or *color additives* under FFDCA (21 U.S.C. § 348) unless they have been determined to be generally recognized as safe (21 C.F.R. § 182.1).

Research products regulated under FFDCA must follow investigational new animal drug (INAD) requirements, which include notification, labeling, record-keeping, and conditions for clinical investigation in animals (21 C.F.R. § 511.1). Product authorization for distribution, sale, and use of the product entails either a pre-market new animal drug approval (NADA) or a conditional approval or indexing under the minor use and minor species sections of FFDCA (21 U.S.C. § 360b, 21 U.S.C. §§ 320ccc–360ccc-1). Drugs must also be manufactured in an approved facility under Current Good Manufacturing Practice regulations to ensure the product's identity, strength, quality, and purity (21 C.F.R. §§ 210–211).

In order for a drug to be authorized for use on food animals, FDA must first establish a tolerance (the maximum residue limit allowed in any edible portion of the animal) for a drug (21 U.S.C. § 360b(a)(6)). To have a tolerance established, drugs used on food animals must be shown to meet stringent safety requirements and to pose extremely low to no risk to humans or other animals when used according to label instructions (21 U.S.C. § 360b(d)(2)). Tolerances for whole meat, poultry, and egg food products are then enforced by the U.S. Department of Agriculture's (USDA) Food Safety and Inspection Service (FSIS) under the Meat Inspection Act (MIA), the Poultry Products Inspection Act (PPIA), and the Egg Products Inspection Act (EPIA), or by FDA for all other food and animal feed under FFDCA. Animals treated with drugs and then slaughtered for food are subject to certification and withholding requirements to ensure the elimination of drug residues (9 C.F.R. § 309.16). Animals used for research investigation into an experimental drug may not be used for food purposes unless they meet the requirements of 9 C.F.R. § 309.17 and 21 U.S.C. § 320ccc-1.

Animal medical devices or veterinary devices are also regulated by FDA CVM under FFDCA. A *veterinary device* is an instrument or other contrivance used on or in animals that is “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease” or “intended to affect the structure or any function of the body of man or other animals,” and, “which does not achieve its primary intended purpose through chemical action within the body of animals and which is not dependent upon being metabolized for the achievement of its primary intended purpose” (21 U.S.C. § 321(h)). Although veterinary devices do not require pre-market approval, they are still subject to some regulatory requirements under FFDCA, such as proper product labeling, even during the research and development phase (FDA OCI 1987). Radiation-emitting devices are also regulated under FFDCA, as amended by the Radiation Control provisions and Medical Device Amendments of 1976, and must be registered with FDA's Center for Devices and Radiological Health (FDA CDRH).

Because the definitions of a drug and a veterinary device under FFDCA are so broad, they encompass most products developed for use on or in vertebrate animals. However, FDA CVM has chosen to not enforce the new animal drug provisions of FFDCA (termed “enforcement discretion”) for particular types of products when FDA CVM has decided these products or devices are adequately regulated under other federal laws and agencies, like certain biological products for animals (discussed below; 21 C.F.R. § 510.4, FDA CVM 2015). FDA CVM will also exercise enforcement discretion under FFDCA on a case-by-case basis when a product poses very low potential risk to the target animals, the public, and the environment (FDA CVM 2015).

Veterinary Biologics

Although also considered to be drugs under FFDCA, products for animals that are categorized as *biological products* (or *veterinary biologics*) are primarily regulated under the Virus-Serum-Toxin Act (VSTA; 21 U.S.C. §§ 151-159 et. seq.), as amended by the 1985 Food Security Act, by USDA’s Animal and Plant Health Inspection Service’s Center for Veterinary Biologics (APHIS CVB) rather than by FDA CVM (21 U.S.C. § 392(b), FDA OCI 1995, APHIS FDA 2013). *Veterinary biologics* are defined as “all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous products at any stage in production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response” (9 C.F.R. § 101.2). The term *treatment* is defined as “the prevention, diagnosis, management, or cure of diseases of animals” (9 C.F.R. § 101.2(3)). The term *analogous products* refers to products that are intended for the treatment of animals, and have a similar function, resemble, or are represented as veterinary biologics (9 C.F.R. § 101.2(2)). Veterinary biologics include vaccines, bacterins, allergens, antibodies, antitoxins, diagnostics, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of microorganisms, and analogous products (9 C.F.R. § 101.2). Diagnostic devices or kits can also meet the definition of a veterinary biologic if they “are intended for use in the treatment of animals through the detection or measurement of antigens, antibodies, nucleic acids, or immunity” (9 C.F.R. § 101.2(2)(ii)). Products that work through an immunological function, but are intended to affect non-disease conditions, like injuries, infertility, or pregnancy, are not regulated as veterinary biologics. The requirement that a veterinary biologic treats a disease of animals does not require that the treated animals themselves suffer any clinical symptoms of the disease, but just that they are a disease carrier or reservoir (APHIS CVB 2005). However, the claims (verbal or written) that can be made for veterinary biologics designed for carrier animals are strictly limited to those that describe the prevention or control of the disease-causing agent in the treated animals only (APHIS CVB 2005).

Regulatory authorization for veterinary biologics entails obtaining a license from APHIS CVB, which is considered tantamount to approval under FFDCA (FDA OCI 1995), and manufacturing the veterinary biologic in a licensed establishment or facility (9 C.F.R. § 102, 21 U.S.C. §§ 151-159 et. seq.). In addition, the transport, import, or use of experimental veterinary biologics in animals must be authorized by APHIS CVB (9 C.F.R. §§ 103-104). Vertebrate animals that are treated with a veterinary biologic and are then used as food or feed for vertebrate animals are subject to

a slaughter withholding period set by APHIS CVB (9 C.F.R. § 309.16, APHIS VS 2015).

No implicit or explicit food safety or human health claims may be made for a veterinary biologic used in food animals (APHIS CVB 2012). Furthermore, no claims may be made that veterinary biologics prevent or control incidence of the disease in humans (APHIS CVB 2005, APHIS FDA 2013). If such claims are made the product will not be regulated as a veterinary biologic by APHIS CVB, but would instead be regulated by FDA (APHIS CVB 2005, APHIS CVB 2012). In addition, because veterinary biologics are also drugs under FFDCa, any unlawful preparation, sale, or transport of unlicensed “veterinary biologics” is still subject to the provisions of FFDCa from which licensed veterinary biologics are exempt, and to regulatory action by FDA CVM (FDA OCI 1995, APHIS FDA 2013).

Pesticides and Pest Control Devices

Most substances designed to have a pesticidal mode of action, which includes competition, inhibition, toxicity, or pathogenicity, against a pest are regulated as *pesticides* under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and FFDCa by the U.S. Environmental Protection Agency’s Office of Pesticide Programs (EPA OPP). A *pesticide* is defined as “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest” (7 U.S.C. § 136(u)). A *pest* is defined under FIFRA as “(1) any insect, rodent, nematode, fungus, weed, or (2) any other form of terrestrial or aquatic plant or animal life or virus, bacteria, or other microorganism (except viruses, bacteria, or other microorganisms on or in living man or other animals)” (7 U.S.C. § 136(t)). The term *insect* in this definition includes the class insect, classes of arthropods, and similar (7 U.S.C. § 136(o)), and the term *nematode* includes the phylum nemathelminths and class nematode (7 U.S.C. § 136(r)). Note that microorganisms on or in animals are not considered pests under FIFRA, so products used on or in vertebrate animals to control microorganisms are not regulated as pesticides. Unless specifically exempted, pesticides must be registered by EPA OPP (7 U.S.C. § 136(a)), and produced by a registered pesticide producing establishment or facility (40 C.F.R. § 167.20(a)) among other regulatory requirements. Some products considered pesticides under FIFRA, could be regulated primarily by FDA CVM and secondarily by EPA OPP depending on their application site, mode of action, if used as aquatic treatments for parasites or disease of aquatic vertebrates, or when the claims made for the product extend beyond those allowed for pesticides (EPA OPP 2016e; EPA FDA 1973). When a product classified as a pesticide targets or is used on vertebrate animals that are used in food products for humans or feed for other animals, EPA OPP also sets a pesticide tolerance (or exemption from a tolerance) as required under FFDCa, as amended by the Food Quality Protection Act (FQPA) (21 U.S.C. § 346a). Like for drugs, tolerances for pesticides in whole meat, poultry, and egg food products are enforced by the FSIS under MIA, PPIA, and EPIA, or by FDA for all other food and animal feed under FFDCa.

During the research and development phase, experimental products are considered unregistered pesticides when they are not yet registered or not registered for the intended use. Laboratory and limited field trials are typically allowed for unregistered pesticides without issuance of an experimental use permit by EPA OPP (40 C.F.R. § 172.3). An experimental use permit is required for larger field trials of unregistered pesticides. Unregistered pesticide products

may not be used in, on, or as food/animal feed unless a tolerance or an exemption from a tolerance has been established under FFDCA for the pesticide (40 C.F.R. § 172.3(c)).

Devices that control pests are *pest control devices* and are also regulated by EPA OPP under FIFRA. Pest control devices are instruments or contrivances (excluding firearms) designed to prevent, destroy, or mitigate that species via physical or mechanical methods, but that generally do not “depend for their effectiveness more upon the performance of the person using the device than on the performance of the device itself” (7 U.S.C. § 136(h), 41 F.R. 225 (November 19, 1976)). Capture devices (or traps) are generally not considered pest control devices under FIFRA when they target vertebrate species. However, there are some exceptions, such as glue traps for mice, which are considered pest control devices like glue traps for invertebrates (41 F.R. 225 (November 19, 1976), EPA OPP 2016b). Pest control devices for vertebrate pest species that are sold independently of pesticidal substances do not require registration with EPA, but are still subject to other regulatory requirements under FIFRA, such as labeling and packaging requirements, registration of the establishment that produces the device, and import and export requirements (19 C.F.R. § 12.112(a), 40 C.F.R. §§ 156-157, 40 C.F.R. § 169, EPA OPP 2016d). However, a device that is packaged and sold together with a pesticidal active ingredient is regulated as a pesticide rather than as a pest control device and is subject to registration requirements (EPA OPP 2016d).

Products consisting of live microorganisms (modified or unmodified) are classified as pesticides when the microorganisms are used as biological control agents against pests under FIFRA (40 C.F.R. § 152.20(a)(3)). In contrast, unmodified macroorganisms (e.g., vertebrates, insect predators, nematodes, macroscopic parasites, and plants) used as biological control agents are exempt from regulation under FIFRA (40 C.F.R. § 152.20(a)(1)). However, if EPA determines that certain biological control agents are not being adequately regulated by other federal agencies, EPA may revoke their exemption and also regulate them under FIFRA (40 C.F.R. § 152.20(a)(2)).

In addition, EPA’s Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA) may also regulate the manufacture, transport, or import of potentially hazardous pesticide intermediates or substances or materials used to synthesize pesticides (EPA OPP 2016c).

Livestock and Plant Pests

Products derived from or consisting of an organism that is considered a pest to livestock under the Animal Health Protection Act (AHPA) are regulated by APHIS Veterinary Services (APHIS VS). The term *livestock* means “all farm-raised animals” (7 U.S.C. § 8302(10)), and includes farm-raised fish. A *pest* under APHA (hereafter, referred to as ‘*livestock pest*’ so that it is not be confused with pest under FIFRA) is defined as “any of the following that can directly or indirectly injure, cause damage to, or cause disease in livestock: (A) A protozoan. (B) A plant. (C) A bacteria. (D) A fungus. (E) A virus or viroid. (F) An infectious agent or other pathogen. (G) An arthropod. (H) A parasite. (I) A prion. (J) A vector. (K) Any organism similar to or allied with any of the organisms described in this paragraph” (7 U.S.C. § 8302(13)). APHIS VS defines the term *vector* to be “all animals (including poultry) such as mice, pigeons, guinea pigs, rats, ferrets, rabbits, chickens, dogs, and the like, which have been treated or inoculated

with organisms, or which are diseased or infected with any contagious, infectious, or communicable disease of animals or poultry or which have been exposed to any such disease” (9 C.F.R. § 122.1(e)). The import, interstate transport, and release of livestock pests requires a permit or the product must be granted nonregulated status by APHIS VS.

Products derived from or consisting of an organism that is considered a *plant pest* under the Plant Protection Act (PPA) are regulated by APHIS Plant Protection Quarantine (APHIS PPQ). *Plant pests* are defined under the PPA as “any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof; viruses; or any organisms similar to or allied with any of the foregoing; or any infectious agents or 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 C.F.R. § 340.1). The genera or taxa that contain plant pests are listed under 7 C.F.R. § 340.2. The import, interstate transport, and release of plant pests requires a permit or the product must be determined to qualify for nonregulated status by APHIS PPQ.

Except for specific biotechnology products where APHIS VS or APHIS’s Biotechnology Regulatory Services (APHIS BRS) will be the primary regulatory agency (discussed below), FDA, EPA, or APHIS CVB will still be the lead regulatory agency for drugs, pesticides, or veterinary biologics derived from or that consist of a known livestock pest or plant pest, but will coordinate their regulatory oversight with APHIS VS or APHIS PPQ (EOP OSTP 1986).

Organisms with Intentionally Altered Genomic DNA

In 1986, multiple federal agencies jointly established the Coordinated Framework for Regulation of Biotechnology (EOP OSTP 1986), which concluded that the regulation of emerging biotechnology, including organisms with intentionally altered genomic DNA (hereafter, IAGDNA for short), would fall under the authority of existing federal laws. Like all other products for vertebrate wildlife management, the characteristics of biotechnology products and how they will be used determine regulatory authority. The sections below describes how the different categories of organisms with IAGDNA are regulated.

Animals with IAGDNA

Animals (members of the animal kingdom) with IAGDNA are regulated separately from any products that are derived or extracted from them, because the intent of IAGDNA is to affect the structure or function of the animal (EOP OSTP 1986, FDA CVM 2015, FDA CVM 2017). Therefore, the IAGDNA within the animal is the article subject to the pre-market approval requirements for new animal drugs under the FFDCA unless exempted by the FDA (EOP OSTP 1986, FDA CVM 2015). Unless FDA exercises enforcement discretion, the IAGDNA within the animal requires a pre-market NADA (EOP OSTP 1986, FDA CVM 2015). However, the FDA has stated that they will exercise enforcement discretion based on whether they believe the animal with IAGDNA is adequately regulated by other laws and agencies, or on a case-by-case basis based on their potential risk (e.g., laboratory animals with IAGDNA used for human disease research or the genetically-engineered glow-in-the-dark aquarium fish; FDA CVM

2015). FDA recommends contacting them as early as possible in the development of animals with IAGDNA. Again, any vertebrate animal with IAGDNA that poses a potential vector risk to livestock under AHPA will also be regulated secondarily by APHIS VS, and FDA will coordinate their regulatory activities with APHIS VS (FDA CVM 2015). FDA CVM will consider invertebrates with IAGDNA on a case-by-case basis to determine if they will be regulated under the new animal drugs provisions of FFDCA, or instead as a pesticide by EPA OPP, a plant pest by APHIS BRS, or a livestock pest by APHIS VS (FDA CVM 2015, FDA CVM 2017).

Microorganisms with IAGDNA

Most potential products consisting of or derived from microorganisms with IAGDNA that are intended to affect the structure of function of vertebrate animals are considered drugs, pesticides, or veterinary biologics (EOP OSTP 1986). For these products that include a plant pest or livestock pest, FDA CVM, EPA OPP, or APHIS CVB will work with APHIS BRS or APHIS VS (EOP OSTP 1986). Microorganisms with IAGDNA used as pesticide intermediates, which are substances or materials used to synthesize pesticides or their active ingredients, that are not used for a pesticidal purpose on their own, are regulated by EPA's Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA) (40 C.F.R. § 725.8, EPA OPP 2016c). All remaining microorganisms with IAGDNA that do not fall into the regulatory categories above are regulated by EPA OPPT under TSCA (EOP OSTP 1986).

Plants with IAGDNA

Most potential products consisting of plants with IAGDNA that are intended to affect the structure of function of vertebrate animals are considered drugs, animal feed, pesticides, or veterinary biologics (EOP OSTP 1986). Plants with IAGDNA that produce pesticides are called plant-incorporated protectants (PIPs; EPA OPP 2016a). For PIPs, EPA OPP regulates the substance produced by a plant and the genetic material incorporated into the plant that gets the plant to produce the substance, but does not regulate the plant itself (40 C.F.R. § 174.3, EPA OPP 2016a). For these products that include a plant pest, FDA CVM, EPA OPP, or APHIS CVB will work with APHIS BRS (EOP OSTP 1986).

DECISION SUPPORT TOOL

The following decision support tool (Figure 1) was developed using publically available documents, including the current U.S. Code and Code of Federal Regulations, agency guidance documents, directives, and website content, and inter-agency memorandums of understanding, and **has not been endorsed or approved by the federal regulatory agencies**. Furthermore, regulatory guidance is subject to change over time. Therefore, researchers and product developers should initiate early conversations with the federal regulatory agencies to verify regulatory jurisdiction over their product and ensure they are in regulatory compliance.

OTHER REGULATORY REQUIREMENTS

Although this decision tool is intended to help identify the primary federal regulatory agency charged with authorizing regulated products designed, manufactured or modified to change the structure of function of the body of a vertebrate animal, it should not be considered exhaustive of all possible federal, state, or local regulatory and permitting requirements that also likely apply to the manufacture, distribution, import, export, sale, use, and disposal of these products and their components. In addition, federal regulatory agencies must also comply with the National Environmental Policy Act and other environmental laws, including the Endangered Species Act, before authorizing products.

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Figure 1. Decision Support Tool. Note: This tool was developed from publically available documents, and has not been approved or endorsed by the federal regulatory agencies. Federal jurisdiction and regulatory requirements should be confirmed with the appropriate regulatory agency early in the product development phase.

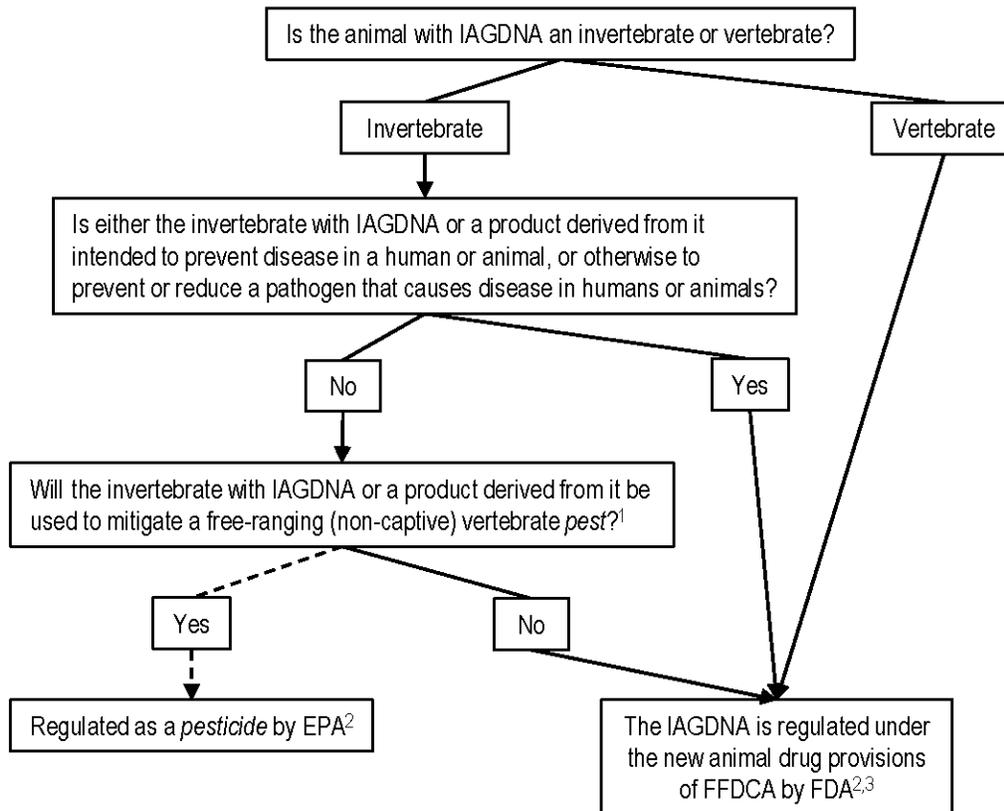
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Into which of the following categories does the product/device fall?

- I. A member of the animal kingdom with intentionally altered genomic DNA (IAGDNA) that is a product or produces a product intended to change the structure or function of the body of another vertebrate animal.
→ Go to Part A of the decision tree for regulation of the animal with IAGDNA. A product extracted or harvested from the IAGDNA animal and intended to change the structure or function of the body of a vertebrate animal is regulated separately, and falls under category I, II, or III below.
- II. A product/device intended to target microorganisms that cause disease in a vertebrate animal.¹
→ Go to Part B of the decision tree.
- III. A product/device intended to target parasites of a vertebrate animal.¹
→ Go to Part C of the decision tree.
- IV. All remaining products/devices intended to change the structure or function of the body of a vertebrate animal.¹
→ Go to Part D of the decision tree.

¹ This part includes products consisting of or derived from plants or microorganisms modified using biotechnology, and products extracted or harvested from IAGDNA animals.

Part A. A member of the animal kingdom with intentionally altered genomic DNA (IAGDNA) that is a product or produces a product intended to change the structure or function of the body of another vertebrate animal.

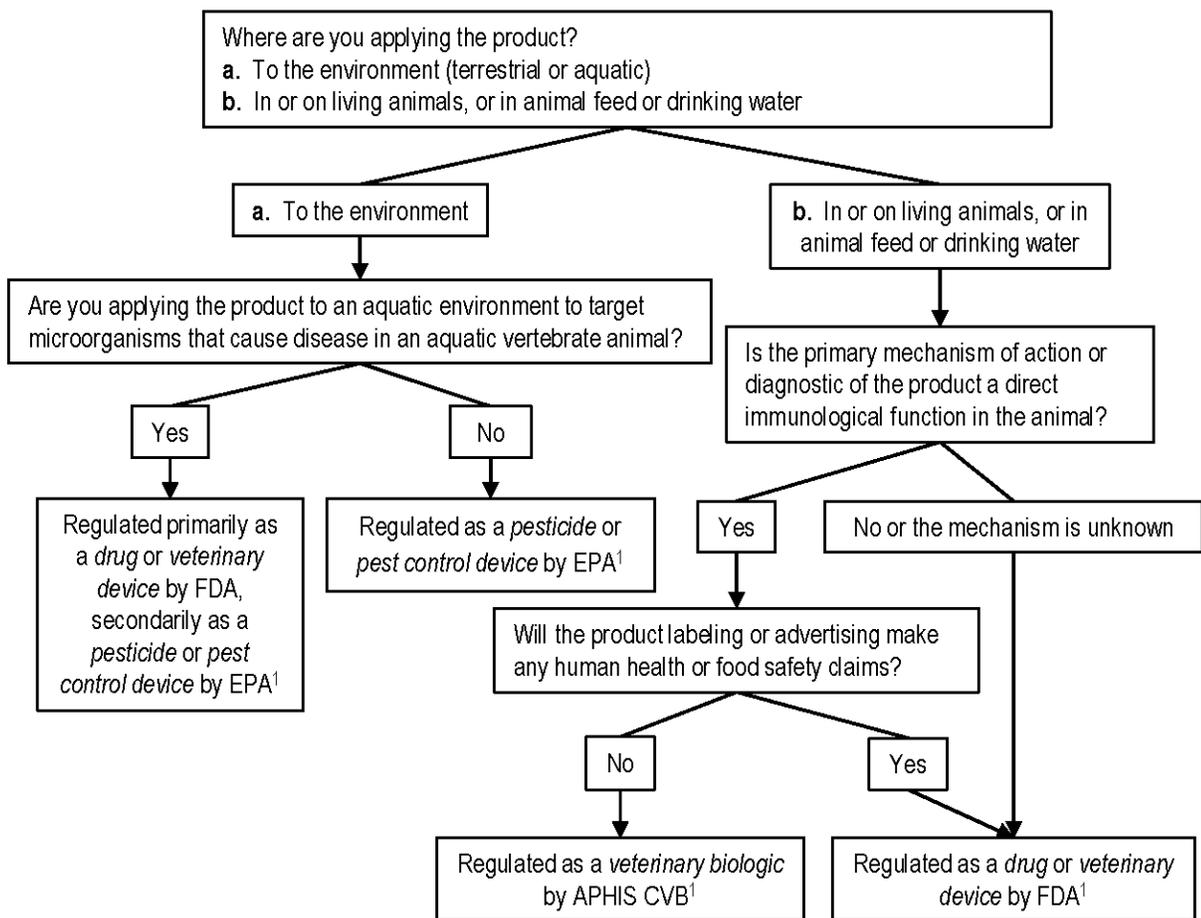


¹ Until further guidance is published, the primary regulatory authority over invertebrates with IAGDNA is going to be decided by FDA and EPA on a case-by-case basis, but could potentially follow the branching represented by dashed lines.

² If either the animal with IAGDNA is derived from or is a potential *livestock pest* or a *plant pest*, the lead regulatory agency will coordinate with APHIS VS or APHIS BRS as they may also regulate the product's importation, interstate transport, or release into the environment.

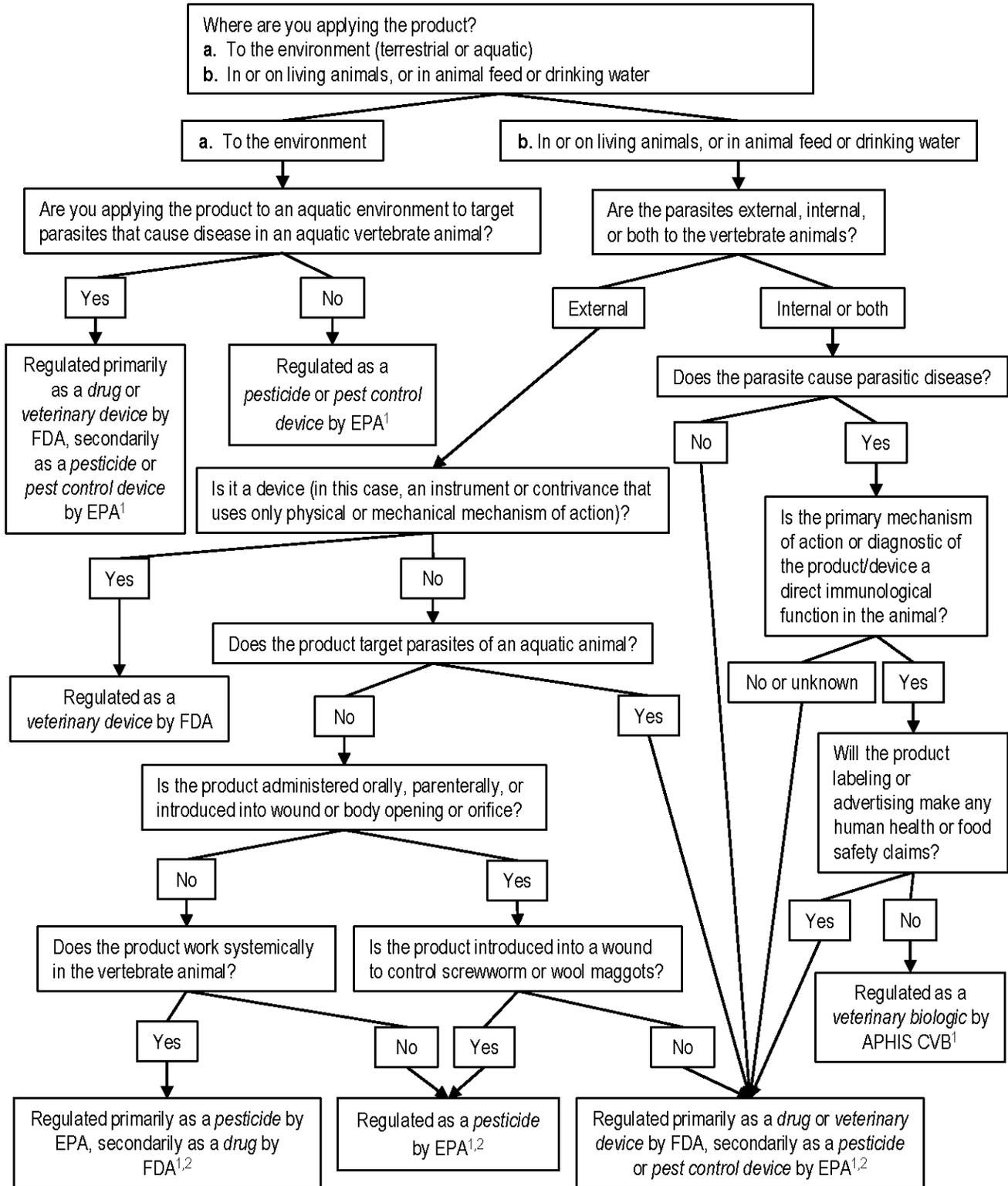
³ Potentially, the IAGDNA in a vertebrate animal could be regulated by either APHIS CVB if it met the definition of a *veterinary biologic* or by EPA if it met the definition of a *pesticide*. However, to date, these agencies have not indicated that they plan to apply the provisions of VSTA or FIFRA to vertebrate animals with IAGDNA.

Part B. A product/device intended to target microorganisms that cause disease in a vertebrate animal.



¹ If the product is classified as or derived from a *plant pest* or a *livestock pest*, APHIS BRS, APHIS PPQ, or APHIS VS may also regulate the product's importation, interstate transport, or release into the environment.

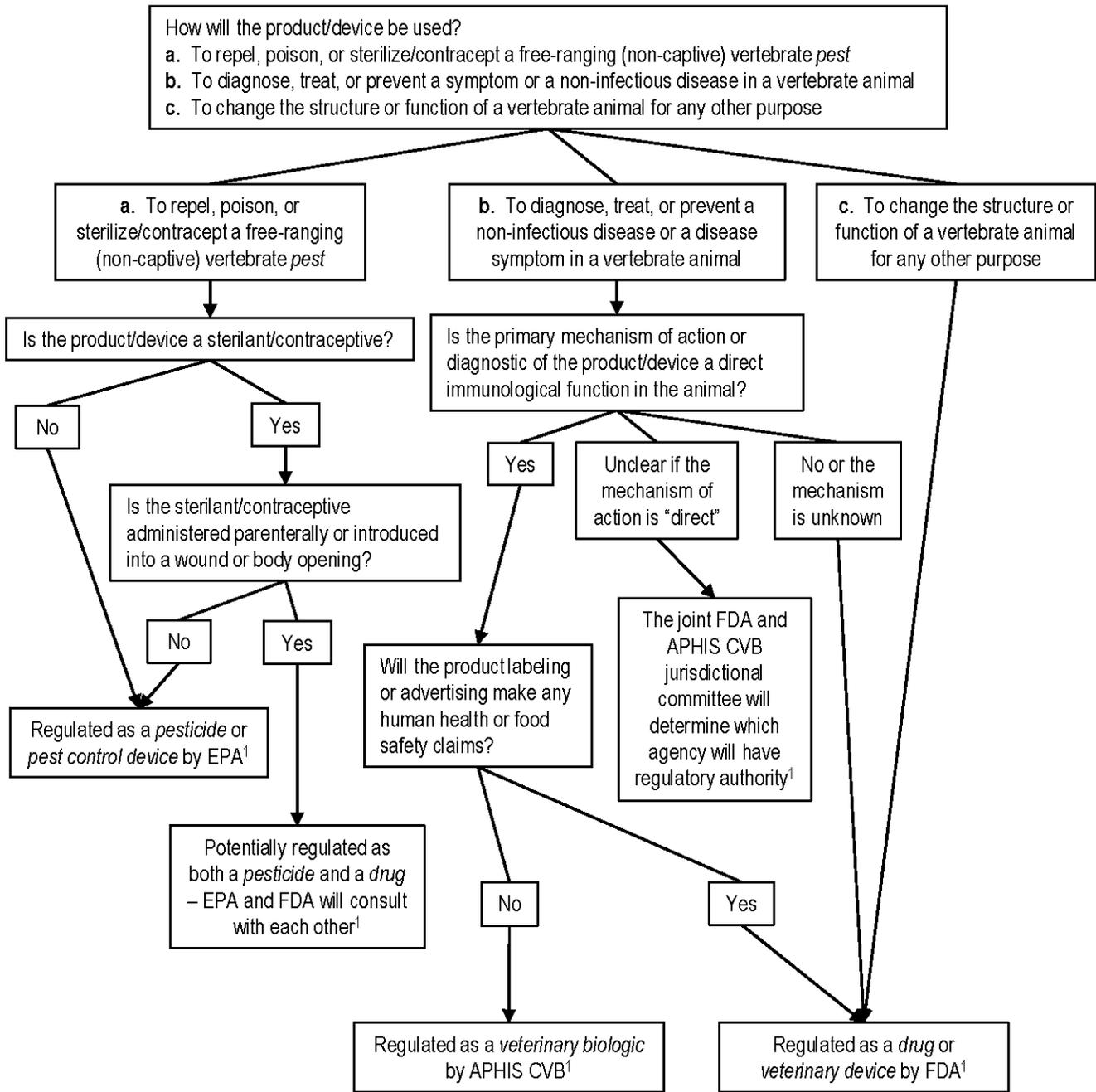
Part C. A product/device intended to target parasites of a vertebrate animal.



¹ If the product is classified as or derived from a *plant pest* or a *livestock pest*, APHIS BRS, APHIS PPQ, or APHIS VS may also regulate the product's importation, interstate transport, or release into the environment.

² For any pesticide product that will be used on or in a vertebrate animal that is then used in food or animal feed, FSIS and FDA enforce tolerances and food additive regulations.

Part D. All remaining products/devices intended to change the structure or function of the body of a vertebrate animal.



¹ If the product is classified as or derived from a *plant pest* or a *livestock pest*, APHIS BRS, APHIS PPQ, or APHIS VS may also regulate the product's importation, interstate transport, or release into the environment.