Vaccines Made from Genetically Modified Organisms

Livestock

Identification of Petitioned Substance

Chemical Names:
Not applicable

Other Name:
GMO vaccines, genetically engineered (GE) vaccines

Trade Names:
Approximately 13 GMO vaccines are registered with the USDA/APHIS Center for Veterinary Biologics for use in livestock animals (see Table 1). Individual vaccine trade names are not identified here.

CAS Numbers:
Not applicable

Other Codes:
Approximately 13 GMO vaccines are registered with the USDA/APHIS Center for Veterinary Biologics for use in livestock animals (see Table 1). Individual registration codes are not identified.

Characterization of Petitioned Substance

Vaccines are administered to livestock species to control infectious diseases, which limit production in animal agriculture and pose disease risk to humans who consume infected animals. Although wild populations are sometimes vaccinated when there is a risk of transmission to humans (e.g., rabies in wild animals), vaccination is more effective in food animals such as pigs, cows, and poultry. Traditional veterinary vaccination involves injection of an inactivated or live (but weakened so as not to cause disease) bacteria or virus strain in addition to various adjuvants. The vaccine causes the animal's body to create antibodies (i.e., white blood cells) that are able to recognize bacteria and viruses and kill them, preventing future disease. The creation of antibodies is called humoral immunity. The benefit of live vaccines is that these vaccines can also trigger cell-mediated immunity, which is required to fight off viruses and bacteria that are able to get inside of host cells, where humoral immunity is ineffective.

In recent decades, advancements in immunology, biotechnology, and many other fields have lead to the development of vaccines produced using genetic engineering technology. Genetic engineering of vaccines includes the process of deleting, adding, or otherwise genetically modifying the viral or bacterial organism used for vaccination. These vaccines include live genetically modified vaccines containing live, weakened strains of the disease; genetically modified inactivated or "killed" vaccines; and DNA vaccines (containing "naked" DNA). As will be discussed in later sections of this report (see Evaluation Questions #4 and #11, and Additional Questions #5, #6, and #7), genetic engineering has been applied to vaccine development to improve upon traditional vaccines in a variety of specific ways. In particular, traditional vaccines have been developed to improve their ability to be tracked in vaccinated animals, reduce viral shedding from animals, increase efficacy against specific diseases, and increase stability during storage and transport.

Composition of the Substance:

GMO vaccines are composed of inactivated or weakened viral or bacterial organisms that have had genetic material added, deleted, or otherwise modified. Vaccines may also contain suspending fluids, adjuvants (additives that help stimulate an immune response, most commonly aluminum salts and oil/water mixtures), stabilizers, preservatives, or other substances to improve shelf-life and effectiveness of the vaccine (CDC, 2011). Additives in GMO vaccines do not differ from conventional vaccines (OIE, 2010).

Properties of the Substance:

This report concerns vaccines, which are biological agents with varying physical properties. In general, GMO vaccines are either live or killed pathogens (viral or bacterial) to which specific modifications, additions, or deletions have been introduced into the pathogen's genome. Types of GMO vaccines are defined further in Additional Question #1 below.

Specific Uses of the Substance:

As described above, vaccines, including GMO vaccines, are administered to livestock species to control infectious diseases.

Approved Legal Uses of the Substance:

Under regulations issued by the USDA's National Organic Program (NOP) pursuant to the Organic Food Production Act of 1990, genetic modification is considered an "excluded method," which is generally prohibited from organic production and handling under 7 CFR 205.105(e). However, the prohibition of excluded methods includes an exception for vaccines with the condition that the vaccines are approved in accordance with §205.600(a). That is, the vaccines must be included on the List of Allowed and Prohibited Substances (hereafter referred to as the National List). At present, the National List identifies all vaccines, as a group, as synthetic substances allowed for use in organic livestock production (7 CFR §205.603(a)(4)). Vaccines are not individually listed on the National List, but rather are included on as a group of synthetic substances termed "Biologics—Vaccines," that may be used in organic livestock production (7 CFR §205.603(a)(4)).

According to livestock health care standards specified in 7 CFR §205.238, organic livestock producers must establish and main preventive healthcare practices, including vaccinations. In addition, 7 CFR §205.238 specifies that any animal drug, other than vaccinations, cannot be administered in the absence of illness. Any animal treated with antibiotics may not be sold, labeled, or represented as an organic (205.238(c)(7)).

Livestock vaccines are regulated by the USDA's Animal and Plant Health Inspection Service (APHIS) Center for Veterinary Biologics under authority of the Virus-Serum-Toxin Act of 1913. In particular, all vaccines used in agricultural animals must be licensed, and vaccines created using biotechnology (i.e., made with GMOs) must adhere to the same standards for traditional vaccines. Specifically, vaccine makers are required to submit a Summary Information Format (SIF) specific to the type of vaccine (Roth and Henderson, 2001). A SIF must present information regarding the efficacy, safety, and environmental impact of the vaccine being registered. The purpose of the SIF is to characterize the vaccine's potential for, and likelihood of, risk. Occasionally, peer-review panels are formed to complete risk assessment of vaccines; this was the case for the currently licensed live vector rabies vaccine (to reduce rabies in wildlife).

Action of the Substance:

The action of vaccines is described in the Characterization of Petitioned Substance section above. Briefly, most vaccines are injected intramuscularly and once inside the body, cause the immune system to create antibodies (i.e., white blood cells) that upon subsequent exposure, are able to recognize bacteria and viruses and kill them (humoral immunity). Humoral immunity can be strengthened by cell-mediated immunity, which involves other types of cells (e.g., "natural killer cells") that are able to fight off viruses and bacteria that enter inside of the animal's cells.

Combinations of the Substance:

As stated above, vaccines may contain suspending fluids, adjuvants, stabilizers, preservatives, or other substances to improve shelf-life and effectiveness of the vaccine (CDC, 2011). In addition, live vector vaccines (see Additional Question #1 for a definition) contain two different viral strains, providing immunity for two diseases in one vaccine. Other non-vector vaccines may contain more than one disease strain as well.

Status

Historic Use:

Vaccines have been used in humans and animals for several hundreds of years. The first documented use occurred in 1798 when Edward Jenner vaccinated humans with cowpox virus to protect them from smallpox. Vaccines utilizing recombinant gene technology did not appear on the market until the mid-1980s. Before the introduction of GMO vaccines, substantial portions of food animals were dying due to infectious disease, even with the use of traditional vaccines and other medical treatments. In 1984, 10% of the 45 million cattle and 15% of 94 million swine born that year died of infectious disease (Faras and Muscoplat, 1985). Growth in the veterinary vaccines industry over the past few decades has been primarily the result of new technological advances, drug resistance by pathogens, and new diseases (Frey, 2007).

OFPA, USDA Final Rule:

In general, the use of genetic engineering is prohibited in organic production and handling. Substances, methods, and ingredients that may and may not be used in organic production and handling are defined in 7 CFR §205.105. Among the provisions of this section is a requirement that organic products must be produced and handled without the use of "excluded methods," which are defined as follows:

> *"A variety of methods used to genetically modify organisms or influence their growth and development by means that are not possible under natural conditions or processes and are not considered compatible with organic production. Such methods include cell fusion, microencapsulation and macroencapsulation, and recombinant DNA technology (including gene deletion, gene doubling, introducing a foreign gene, and changing the positions of genes when achieved by recombinant DNA technology). Such methods do not include the use of traditional breeding, conjugation, fermentation, hybridization, in vitro fertilization, or tissue culture. "* (7 CFR §205.2)

However, vaccines are specifically excluded (7 CFR §205.105(e)) from the prohibition of excluded methods, provided that the vaccines are approved for use by inclusion on the National List. At present, the National List identifies all vaccines, as a group, as synthetic substances allowed for use in organic livestock production (7 CFR §205.603(a)(4)). Vaccines are not individually listed and no distinction is made between vaccines made with and without the use of genetic engineering. This has led the NOP to suggest that the NOSB review GMO vaccines as a class of materials according to the provisions at §206.600(a) (OMRI, 2011). Livestock vaccines also are regulated by the Center for Veterinary Biologics, within USDA's APHIS, under authority of the Virus-Serum-Toxin Act of 1913.

International

The Canadian Food Inspection Agency (CFIA) regulates veterinary biologics in Canada. Vaccines and vaccine manufacturing facilities are licensed pending an initial evaluation of the vaccine product. The CFIA prepares an environmental assessment for all GMO vaccines that discusses the vaccine's safety to the target animal, non-target animals, humans, and the environment.

However, GMO vaccines are not allowed in organic agriculture in Canada. The list of permitted substances for organic agriculture indicates that veterinary biologics, including vaccines, may not utilize "organisms from genetic engineering or their products (e.g., recombinant gene technology)" (CGSB, 2009).

According to the Codex Alimentarius Commission's guidelines for organic agriculture, "where specific disease or health problems occur, or may occur, and no alternative permitted treatment or management practice exists, or, in cases required by law, vaccination of livestock, the use of parasiticides, or therapeutic use of veterinary drugs are permitted." The standards do not clarify whether vaccines should be free of

GMO organisms; however, it is noted in the guidelines that anything contained in animal feed must be from non-biotechnology-derived sources (Codex Alimentarius Commission, 1999).

In the previous organic standards in Europe, GMO vaccines were allowed exceptions to the general ban on genetically modified products (EC No. 2092/91). However, the updated EU standards (EC No. 834/2007 and 889/2008) do not explicitly discuss GMO vaccines.

According to the International Federation of Organic Agriculture Movements (IFOAM) draft 2010 standards, while "the deliberate use or negligent introduction of genetically engineered organisms or their derivatives is prohibited" for animals, seeds, fertilizers, and other materials, IFOAM makes an exception for vaccines (IFOAM, 2010).

Recombinant technology is generally prohibited in the production of livestock products under the Japan Agricultural Standard (JAS) for Organic Production; however, a discussion of vaccines derived with GMO organisms is not provided (JMAFF, 2005).

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1: What category in OFPA does this substance fall under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

The substance is a medicinal product used to prevent illness in food animals. It does not fall under EPA List 4.

Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

Vaccines are composed of either weakened live or killed pathogens from a variety of sources. The production process begins when the virus/bacteria are replicated from a "reference" organism and grown in a protein growth medium (viruses are grown on a bovine kidney cell line or in chicken eggs, and bacteria are grown in bioreactors) in the laboratory (DHHS, 2005). After replication, the pathogens are inactivated, killed, and/or modified, depending upon the vaccine being created. Traditionally, live vaccines are weakened by passing them through the laboratory host system. Alternatively, pathogens can be inactivated using one or more chemicals. Other vaccines are created by extracting and purifying a particular part of the pathogenic organism (CAST, 2008). As explained in the Characterization of Petitioned Substance section above, GMO vaccine production differs from traditional vaccine production in that GMO vaccine organisms are altered by deleting, adding, or otherwise genetically modifying the bacteria or virus.

Evaluation Question #3: Is the substance synthetic? Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Yes, vaccines produced using genetically modified organisms are classified as synthetic. According to the current National List, these vaccines are synthetic substances allowed for use in organic livestock production (7 CFR §205.603(a)(4)). While they are derived from naturally-occurring pathogens, vaccines

are produced by replication in the laboratory. In addition, chemicals may be used to inactivate live pathogens and/or added to the final product for preservative or enhancement purposes (CAST, 2008).

Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

GMO vaccines are not expected to persist in the environment any longer than traditional vaccines. CFIA (2007 and 2008a) stated that any pathogenic bacteria created from gene transfer would be unable to persist in the environment for long periods of time. While viruses or bacteria shed from vaccinated animals may survive in the environment for a short time, the amount of shed pathogen is generally low and may not be excreted from all vaccinated animals. A safety assessment of a human *V. cholera* live genetically modified vaccine indicated that the shedding of pathogenic vibrios from GMO vaccine-inoculated patients was considerably less than patients administered the non-GMO vaccine strain and that the GMO vaccinated patients shed 10^6 to 10^8 times fewer vibrios than those infected with cholera. Furthermore, shedding occurred in only 20-30% of patients inoculated with the GMO vaccine for a maximum of 7 days (Frey, 2007). It is also advantageous that gene-deleted GMO vaccines (e.g., bovine rhinotracheitis, pseudorabies, and classical swine fever vaccines) can be tracked in the environment, as the survival of the organisms in the animal and the environment can be investigated during GMO strain construction. However, vaccines with inactivated (rather than deleted) pathogens cannot be tracked in this way because both vaccinated and infected animals will produce the same antibodies against the disease (Frey, 2007).

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

All vaccines (conventional and GMO) can be shed in the animal's feces and other secretions, although not all animals will shed vaccine DNA. This shed DNA could potentially infect other animals and spread the virus or bacteria in the environment. However, as discussed in Evaluation Question #4, vaccines cannot survive in the environment for long periods of time. Vaccines contain aluminum salts and other chemical adjuvants or additives; however, it is unclear if these substances are released in high quantities or whether they may impact the environment. Moreover, for both conventional and GMO vaccines, regulatory authorities consider additives when licensing them, establishing residue limits and withdrawal periods (required time between vaccination and slaughtering or milking) when necessary (OIE, 2010).

Evaluation Question #6: Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

Although accidental spills may occur during vaccination and some environmental contamination may occur during proper use (e.g., in coarse spray vaccine administration), as discussed in Evaluation Question #4, extensive contamination of the environment with vaccine organisms is not anticipated due to low rates of shedding and the low survival rate of many pathogens in the environment (CFIA 2007 and 2008a). If manufacturers/livestock farmers do not correctly dispose of unused or expired vaccine materials, there is a potential for contamination of the environment with vaccine additives such as mercury-containing thimerosal (MDH, 2011). The impact of this contamination would depend on the specific circumstances of the manufacturing process or disposal.

Evaluation Question #7: Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

Vaccine additives may interact with other additives/adjuvants; however, reactions are limited due to the generally small amounts of chemical constituents present in vaccines. Furthermore, preservative/adjuvant combinations such as thimerosal and aluminum salts are common, and generally any vaccines causing adverse reactions would not be allowed on the market unless risks were mitigated (Roth and Henderson, 2001).

Because some vaccines (e.g., influenza and yellow fever vaccines) are produced with egg products, people with allergies may have allergic reactions to them (CDC, 2011). For the same reason, additives in livestock vaccines could cause allergic reactions in inoculated animals; however, these reactions should not differ based on the vaccine's status as GMO or conventional.

Vaccines may also interact with each other (termed "vaccine-vaccine interactions"), which can reduce the efficacy of one or both vaccines or cause adverse effects. Otto et al. (2007) studied the possible interactions between *Haemophilus influenzae* type b (Hib) and meningococcal group C (MenC) conjugate vaccines, used in humans; results indicated that the two vaccines did not degrade each other or induce significant interactions (Otto et al., 2007). Studies on the other potential vaccine-vaccine interactions involving GMO vaccines have not been identified.

Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil) crops, and livestock (7 U.S.C. § 6518 (m) (5)).

GMO vaccines are meant to improve immunity to disease in vaccinated livestock animals. There are vaccines that are used to control reproduction (Meeusen et al., 2007), but these should be evaluated separately from vaccines intended to control disease.

All vaccines, including GMO vaccines, can cause unwanted side effects in vaccinated animals including swelling and irritation at the site of injection, fever, coughing (after nasal administration), respiratory distress, and reduced fertility (Morton, 2007). However, there is no difference in these symptoms between GMO and traditional vaccines, and all vaccines are evaluated for side effects by manufacturers.

Evaluation Question #9: Discuss and summarize findings on whether the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

Because live vaccine pathogens cannot survive long outside of a host, environmental damage is not expected from accidental release or shedding from vaccinated animals. Furthermore, although there is a possibility that non-target species in close proximity to vaccinated animals may become infected with pathogens from vaccine shedding, studies have indicated that this has not been a problem historically. Once again, the ability for the pathogen to spread is limited by its short lifespan in the environment. In addition, some GMO vaccines have been tested in non-target species (e.g., the GMO *Salmonella typhurium* vaccine in rats, mice, calves, and pigs) and have not shown to adversely affect these species (CFIA, 2006).

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

Regulators have noted that farmers or vaccine applicators could become infected during care of vaccinated animals that shed viral or bacterial organisms (CFIA, 2007 and 2008a). However, many of the diseases for which food animals are vaccinated cannot reproduce in either the target animal or humans (CFIA, 2007 and 2008a). For example, the vector for the porcine circovirus vaccine is Baculovirus, which is an insect virus not associated with disease in humans or animals. Risk assessments for GMO vaccines conducted by the Canadian Food Inspection Agency (CFIA) predicted that human health effects in workers would be minimal, as long as handlers took the necessary safety precautions to protect themselves (e.g., safety equipment such as gloves).

Some regulators and scientists have questioned whether the meat from GMO vaccinated animals may be harmful to humans who consume it (CFIA, 2006; Traavik, 1999). This issue is examined before licensure of a GMO vaccine. For example, the risk assessment report from the CFIA (2006) indicates that the *Salmonella typhurium* vaccine (live culture GMO vaccine) has a low health risk to humans exposed through spills or shedding by vaccinated animals. The vaccine strain is entirely eliminated before the broiler chickens are sold, so salmonella exposure to humans consuming vaccinated animals is unlikely. If any viral DNA is left

in meat from vaccinated animals, it is expected to be broken down in the human gastrointestinal tract, thus, health problems are not anticipated from consumption (CFIA, 2010).

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Organic livestock producers may choose between traditional and GMO vaccines when treating for most diseases (See the "OFPA, USDA Final Rule" section above for further discussion of the regulatory status of traditional and GMO vaccines.) However, there are some diseases or combinations of diseases for which a GMO vaccine is the only available product (Foley, 2011). For example, there is no conventional Avian salmonellosis vaccine and there is no conventional combination vaccine for Fowl Pox and *Mycoplasma Gallisepticum* (note that there are conventional vaccines available for the two diseases separately) (USDA, 2011). In addition, the number of available GMO vaccines and conventional vaccines vary with time due to new license issues and previous license terminations on an ongoing basis. It should also be noted that GMO vaccines are sometimes safer, and often more efficacious and cheaper than their traditional counterparts (Shams, 2005; see Additional Question #7).

Homeopathic remedies may also be used to supplement or replace vaccines. For example, nosodes are a homeopathic remedy made from a pathological product (e.g., blood, saliva, or diseased tissue) that are administered orally (ECCH, 2008). Nosodes act similarly to vaccines by facilitating natural resistance mechanisms and increasing the cure rate of existing infections in animals. However, some studies have indicated that nosodes are not highly efficacious in preventing disease (McCroy and Barlow, in Morris and Keilty, 2006). Natural herbal supplements like dandelion and chicory may also be used, but these are usually used to treat infection once it occurs, rather than to prevent infection (Morris and Keilty, 2006).

Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Vaccines are an integral part of animal agriculture to prevent disease and animal suffering (Morton, 2007). It is unlikely that homeopathic or other methods would render vaccinations unnecessary. However, as explained in Evaluation Question #11, many traditional vaccines can be used in place of GMO vaccines for common diseases.

Additional Evaluation Questions for GMO Vaccines Used in Livestock

Additional Question #1. What constitutes a GMO vaccine; i.e., are there different levels of GMO use that could determine if a vaccine is labeled GMO?

GMO (genetically modified organism; also commonly referred to as genetically modified [GM] or genetically engineered [GE]) vaccines include all of those vaccines in which specific modifications, additions, or deletions are introduced into the viral or bacterial genome. These vaccines can be made of either live or killed pathogens. Specific types of GMO vaccines include:

- **Gene-deleted vaccines** have a gene deleted or inactivated. **Marker vaccines** are a type of gene-deleted vaccine that allow differentiation from field strains for diagnostic purposes (e.g., foot and mouth disease vaccines),

- **Subunit vaccines** from isolated genes, which contain only part of the virus' or bacteria's DNA (e.g., the vaccine for post-weaning multisystemic wasting syndrome in swine), including c**himeric virus vaccines**, which combine parts of genes from more than one type of virus (examples: recently developed poultry avian influenza vaccine),

- **Vector vaccines** contain live virus or bacteria strains that have been injected with a protective gene from another disease agent. These vaccines protect against both the host virus/bacteria and the injected virus/bacteria,

- **DNA vaccines** are made up of "naked" DNA (in other words, the DNA has been removed from the bacterial or viral organism), which is directly injected into the animal (not currently used for livestock animals).

A 2010 report by the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO), and the World Health Organization (WHO) suggested that animals vaccinated with GMO vaccines should not be considered GM animals (OIE, 2010). Further, they clarified the difference between GM foods and the use of GMO vaccines. With engineered foods, the intention is to introduce a new trait into a food; this trait will be present in the food eaten by the consumer. On the other hand, the intention of genetically modified vaccines is to introduce into food animals "a protective immune response by means of an immunogen that is often no longer itself present at the time the animal is slaughtered." However, OIE noted that this is a generalization and there may be exceptions. It recommended that each vaccine should be evaluated independently for risk.

There do not appear to be different "levels" of GMO use in vaccines; all examples described above use some form of genetic engineering.

Additional Question #2. Are there [livestock] diseases that are only covered with GMO vaccines?

Yes. According to sources at the USDA Center for Veterinary Biologics (Foley, 2011), a GMO vaccine is the only option available for some diseases or combinations of diseases in food animals. For other diseases, conventional and GMO vaccines are available. However, the number of available GMO and conventional vaccines vary with time due to new licenses and previous license terminations on an ongoing basis. See Additional Question #3 for more information.

Additional Question #3. What is the proportion of GMO/non-GMO vaccines currently available [for livestock]?

According to the USDA Center for Veterinary Biologics (2010) and Foley (2011), approximately 73 vaccines are licensed for use in wild and domesticated animals as of September, 2010. Of these, 28 are GMO vaccines (about 39%) and 13 (about 18%) are given to livestock animals (e.g., the *Escherichia Coli* bacterin-toxoid for neonatal diarrhea in swine and the Newcastle disease-fowl pox vaccine with live fowl pox vector for use in poultry). Because organic certifying agents generally do not consider GMO status, no data are available on how many GMO vaccines are being used in organic production at this time. However, Frey (2007) stated that conventional, non-GMO live bacterial vaccines are still used extensively and that GMO live bacterial vaccines are still very rare in veterinary medicine (Frey, 2007). GM viral vaccines are more prevalent than GM bacterial vaccines, although there remain many conventional viral vaccines. See Table 1 for a list of selected conventional and GMO vaccines.

Table 1. Selected Conventional and GMO Vaccines Used for Food Animals[a]

Disease	Conventional vaccine/strain	GMO vaccine/strain
Bacterial		
Brucellosis (ruminants)	*Brucella abortus*, strain 19, strain RB51	None identified
Brucellosis (swine)	*Brucella suis*, strain 2	None identified
Anthrax (bovine, ovine, equine)	*Bacillus anthracis*, strain Sterne	None identified
Johne's disease	*Mycobacterium paratuberculosis* strain 316F	None identified
Contagious bovine pleuropneumonia	*Mycoplasma mycoides* subsp. *mycoides* SC, strain T1/44	None identified
Avian salmonellosis	*Salmonella enteric* servo. Gallinarium, strain R9	*Salmonella typhimurium* vaccine, live culture

Table 1. Selected Conventional and GMO Vaccines Used for Food Animals[a]		
Disease	**Conventional vaccine/strain**	**GMO vaccine/strain**
Bovine salmonellosis	None identified	*Salmonella dublin* vaccine
Poultry cholera	*Pasturella multocida* (various strains)	None identified
Cattle pasteurellosis	Manheimia (*Pasteurella*) *haemolytica* (various strains)	None identified
Swine atropic rhinitis	*Bordetella bronchiseptica* (various strains)	None identified
Bovine clostridiosis	*Clostridium perfringens*	None identified
Escherichia Coli in poultry	*Escherichia coli* vaccine, avirulent live culture	*Escherichia coli* vaccine, live culture
Viral		
Avian encephalomyelitis	Live and modified live virus	Avian encephalomyelitis-fowl pox-laryngotracheitis vaccine
Porcine circovirus (swine)	Type 2, killed virus	Porcine circovirus vaccine (Type 1 -Type 2 chimera, killed virus; and Type 2 killed, baculovirus vector)
Marek's disease (poultry)	Live strains of Marek's disease virus, serotypes 1, 2, or 3	Marek's Disease-Newcastle Disease live virus vaccine, Serotypes 1 & 2 & 3, live Marek's disease vector; and Marek's disease live herpesvirus chimera
Newcastle disease (poultry)	Bursal-disease-newcastle disease-bronchitis vaccine, killed or live virus; live virus VG/GA strain; killed virus; and B1 type, B1 strain live virus	Newcastle disease-fowl pox vaccine, live fowl pox vector; and Marek's disease-Newcastle disease vaccine, serotype 3, live Marek's disease vector
Bursal disease (poultry)	Live or killed avian *bursitidis infectivae* virus type 1	Bursal disease-Marek's disease vaccine, Serotype 3, live Marek's disease vector
Fowl pox	Live fowl pox vaccine	Fowl pox-laryngotracheitis vaccine, live fowl pox vector
Fowl laryngotracheitis	Modified live virus vaccine	Fowl pox-laryngotracheitis vaccine, live fowl pox vector

[a]Sources: Frey (2007); USDA (2011)

<u>Additional Question #4</u>. Are there effective alternative(s) to GMO vaccines, such as a combination of conventionally produced vaccines, nosodes, etc.?

According to the European Council for Classical Homeopathy (ECCH), nosodes are "homeopathic remedies of biological origin that are derived from pathologically modified organs or parts of organs that are of human or animal origin, or from cultured micro-organisms that have been killed, or from products of the decomposition of animal organs, or from body liquids containing pathogens or pathological products" (ECCH, 2008). Nosodes act similarly to vaccines by facilitating natural resistance mechanisms

and increasing the cure rate of existing infections in animals. Nosodes have been used to treat bovine mastitis, or inflammation of the mammary glands, in dairy cows. This condition is usually caused by bacteria entering the udder. Vaccines have been shown to be ineffective in preventing most cases of mastitis. However, *E. Coli* J-5 vaccine for *E-Coli*-caused mastitis can decrease the severity of the condition (McCroy and Barlow, in Morris and Keilty, 2006). In a randomized study by McCroy and Barlow (performed in 1997, reported in 2006), over 1,000 cows and 300 calves were studied for the effect of nosodes on bovine mastitis and calf scour (diarrhea). The authors reported that the treatment with nosodes did not alter the incidence in new cases of mastitis, compared to controls. Authors did not investigate how nosodes affected severity of mastitis infection. In addition, the *E. coli* nosodes did not reduce the incidence of scour in calves (McCroy and Barlow, in Morris and Keilty, 2006). This report indicates that nosodes alone were not effective in reducing the incidence of mastitis or calf scour in the population studied.

However, nosodes may be more effective if combined with conventional vaccines or if other homeopathic remedies are used. A study by Werner et al. (2010) found no difference between the cure rates of homeopathic treatments versus antibiotic treatments (allowed in conventional livestock only) for mild to moderate mastisis at the end of a 56-day treatment period. However, authors reported that the homeopathic remedy significantly increased the cure rate compared to placebo treatments. The antibiotic treatment consisted of cloxacillin followed by cefquinom and the homeopathic treatments were tailored to the treated animals based on their symptoms and included oral doses of *Phytolacca decandra* (poke root), *Bryonia alba* (white byrony plant), *Pulsatilla pratensis* (small pasque flower), *Mercuris solubilis* (mercury/quiksilver), *Hepar sulfurus* (calcium sulphide), and *Apis mellifica* (made from honey bees). Despite the improvements compared to placebo-treated animals, authors noted that both homeopathic and antibiotic treatments had a relatively low cure rate, suggesting low efficacy for these two treatments (Werner et al., 2010).

No other nosodes or homeopathic remedies were identified for use in food animals.

Additional Question #5. Studies on the potential harm from the use of GMO vaccines.

Studies concerning the potential harm from GMO vaccines are described below. It is important to note that there are various forms of GMO vaccines with different safety concerns; each vaccine has its own safety considerations as well. For example, many GMO vaccines, including live canarypox vector vaccines in horses and live Marek's disease vector vaccines in chickens, are derived from existing disease strains that have been used in conventional vaccination for a long period of time. A record of safe use of the disease strain in the past improves the expected safety of the genetically modified version of the vaccine (OIE, 2010).

One of the concerns commonly expressed over the safety of GMO vaccines is the possibility that the non-pathogenic (not able to cause disease) strain present in the vaccine may mutate or combine with other genes to become pathogenic (virulent; disease-causing) after administration (Traavik, 1999; Roth and Henderson, 2001). While this can happen with both conventional and genetically modified vaccines, the likelihood depends upon the type and the specific characteristics of the vaccine (see below). With bacterial GMO vaccines (which are predominantly administered via the mouth), there are concerns that the engineered bacteria may recombine with natural bacteria in the gastrointestinal tract. Furthermore, it is unclear how long the altered virus/bacteria will remain in the vaccinated animal (Traavik, 1999).

Another general concern for GMO vaccines made from live virus or bacteria is the shedding of DNA from vaccinated animals. All vaccines (conventional and GMO) can be shed in the animal's feces and other secretions, although not all animals will shed vaccine DNA. This shed DNA could potentially infect other animals and spread the virus or bacteria. Theoretically, shed viral DNA in the environment may recombine with naturally occurring viruses, forming altered virus strains with unpredictable characteristics. The biological and ecological consequences of such changes are difficult to predict, but could be harmful (Traavik, 1999). However, with GMO vaccines, it is possible to locate the mobile, active gene elements needed to cause disease and delete or inactivate them. For example, with the cholera vaccine *V. cholerae* CVD 103-HgR, developers deleted 95% of both chromosomal copies of the *ctxA* gene,

which is responsible for its toxicity. The advantage to pathogen gene deletion is that it decreases the likelihood of gene transfer from live vaccine to other organisms (Frey, 2007). Risk assessment during strain construction should consider these factors and each vaccine's ability to be traced in the environment. Below is a summary of potential advantages, disadvantages, and safety concerns for each of the major GMO vaccine types.

Gene-deleted Vaccines

Gene-deleted vaccines made from live or killed virus are created using organisms that have had specific gene(s) deleted or rendered inactive. The development of these vaccines means that the genetic basis for reduced virulence is understood, which allows researchers to predict and/or monitor the ability of the vaccine to revert to virulence. Like subunit vaccines, genes that induce immune suppression or hypersensitivity to the vaccine can be deleted, improving vaccine safety. Gene-deleted vaccines are also used for the production of marker vaccines, which allow for the identification of animals that have been vaccinated. Gene-deleted vaccines and companion diagnostic tests have been developed for pseudorabies virus in swine, bovine herpes virus I in cattle, and classical swine fever virus (hog cholera). Although gene-deleted vaccines may interact with the virulent organism in the animal, thus restoring the disease-causing ability of the organism, the genetically modified organism should not be any more virulent or pathogenic than the strain found in the environment. The exception is if two gene-deleted organisms in the same animal recombine to form a disease strain the animal did not previously have. This emphasizes the need to have the same deletion in all gene-deleted vaccines for a specific organism (Roth and Henderson, 2001).

Subunit Vaccines

Subunit vaccines contain only a portion of the infectious, disease-causing agent (e.g., only parts of a virus' proteins). Roth and Henderson (2001) indicate that these vaccines are relatively safe, efficient, and inexpensive. An important advantage is the ability to remove or weaken the immunological gene processes that cause hypersensitivity reactions to the vaccine. Disadvantages of subunit vaccines include limited immune protection because these vaccines only express a few antigens[1]. Subunit vaccines also require the use of adjuvants, or additives, to increase the immune response. Use of adjuvants can result in a higher likelihood of adverse reaction to the vaccine.

Live Vector Vaccines

Live vectored vaccines are produced by placing genes that code for a protective antigen into another organism (the vector); this organism then replicates (makes copies) and expresses the antigen in the vaccinated animal. These vaccines have been developed for viruses and bacteria. One of the most important advantages is the ability to administer live vectored vaccines through the nose (intranasally) or in the mouth (intraorally) rather than by injection under the skin, as is done for most vaccines. Vectored vaccines contain pathogens that have had their genetic material deleted or inactivated. They do not have the potential, like conventional modified vaccines do, to revert to virulence or cause disease in vaccinated animals with suppressed immune systems. Live vector vaccines may also be able to overcome the interference with immune response caused by the maternal antibodies young animals inherit from their mother (a difficult task for many pathogens). Roth and Henderson (2001) emphasize that live vectored vaccines must be engineered without the use of markers (strands of DNA) that are resistant to antibiotics in the vaccine organism. These resistant organisms are commonly used in helping to select organisms to use as vaccine vectors, but they could reduce the efficacy of antibiotics used to treat illness. Licensed viral vector vaccines include a rabies vaccine (with a vaccina virus vector) and Newcastle disease vaccine (with a fowl pox vector).

[1] Any substance that stimulates an immune response in the body (especially the production of antibodies)

DNA Vaccines

DNA vaccines consisting of purified recombinant DNA (artificial DNA created by combining several sequences of DNA) are somewhat different than other GM vaccines. Only a few live DNA vaccines have been formulated, and so far none are registered for food animals. It is difficult to illicit the same immune response in all animals given DNA vaccines (Roth and Henderson, 2001). The OIE concluded that these vaccines would not pose a significant food safety risk if used, as only low amounts of administered DNA would be present in vaccinated animals at the time of slaughter and any DNA left in the tissue would be rapidly degraded during digestion (OIE, 2010). Furthermore, these vaccines cannot revert to virulence nor become virulent in animals with suppressed immune systems that are given the vaccine (Roth and Henderson, 2001). However, there is some concern that DNA from these vaccines may integrate into a host's chromosomes and initiate a cancer-initiating event, although results have been negative in experiments thus far (European Commission, 1999). In addition, the modified DNA could theoretically integrate into the sperm or egg cells and be passed on to future generations.

Case Studies of Select GMO Vaccines Currently Licensed in the United States

The Canadian Food Inspection Agency (CFIA) has posted online a number of risk assessments of GMO vaccines performed by the agency for the purpose of licensing. The following is a summary of the safety concerns covered in the assessment of a live vector vaccine for laryngotracheitis-Marek's disease (serotype 3; Marek's disease vector). This vaccine has been licensed in the U.S. since 2007.

Fowl laryngotacheitis is a contagious respiratory disease mainly infecting chickens in commercial layer and broiler flocks. Marek's disease is a widespread viral, cancer-causing disease of poultry, which is difficult to remove once flocks have become infected because it spreads easily and quickly. Vaccination does not prevent the disease, but reduces shedding and thus spread of the virus.

CFIA (2010) discussed the theoretical risk of horizontal gene transfer (when an organism incorporates genetic material from another organism) of this particular vaccine, saying that the risk was low based on existing in vitro and in vivo data. Furthermore, the risk of recombination of the virus, allowing it to become virulent again, was considered low, based on other studies of similar viruses (not cited). CFIA (2010) also reported that in vivo studies conducted by the manufacturer indicated that the virus could not replicate in any other avian species besides chickens and turkeys, and that there was no transmission of the GMO between vaccinated and unvaccinated chickens. Shedding of the GMO would be mostly contained to the indoor environments of the chickens, although risk from accidental spills and release of vented air may allow for some spread of the GMO to the outdoor environment.

In considering the safety of the GMO vaccine for humans, CFIA (2010) evaluated the potential for exposure to humans through consumption of the meat of vaccinated birds. Exposure would be low because the virus is localized to visceral organs and feather follicles, which are not commonly consumed. In addition, any trace amounts of viral DNA present in the consumed meat would be digested in the gastrointestinal tract. Any exposure that did occur was not expected to cause adverse human health effects. The report concluded that no significant public health issues were expected to result from widespread use of the vaccine.

The CFIA has performed similar risk assessments for the *Salmonella typhurium* vaccine (live culture); the porcine circovirus vaccine, type 1/type 2 chimera (killed virus); the porcine circovirus vaccine type 2, killed Baculovirus vector; the bursal disease – Marek's disease vaccine, serotype 3, live Marek's disease vector; and the *Escherichia coli* live culture vaccine.

The *Salmonella typhurium* vaccine (live culture) is used for immunization of healthy chickens in order to reduce the colonization of *Salmonella typhurium* bacteria in internal organs. The report from the CFIA (2006) indicates that the vaccine has a low health risk to humans exposed through spills or shedding by vaccinated animals. The vaccine strain is entirely eliminated before the broiler chickens are sold, so salmonella exposure to humans consuming vaccinated animals is unlikely. Studies also show that

reversion to virulence has not occurred in the vaccine and no safety concerns have been reported in over 10 years of use (primarily in the United States and Germany). Finally, there are no additives or adjuvants in this vaccine, reducing the potential risk associated with these ingredients.

The porcine circovirus vaccines are used to prevent porcine circovirus type 1 (PCV1) and/or type 2 (PVC2), which are associated with post-weaning multisystemic wasting syndrome in swine. The killed Baculovirus vector vaccine and the chimeric vaccine were evaluated separately by the CFIA (2007 and 2008a). Authors reported no concerns with the chimeric vaccine in either animals or humans; studies in pigs and guinea pigs have showed no adverse reactions and there have been no reports of human disease from porcine circovirus. Both forms of the vaccines contain inactivated, or "killed" virus, further reducing their transmission risk. The CFIA reported that the porcince circovirus vaccine, type 2, killed Baculovirus had "acceptable" levels of adverse effects in pigs and as with the chimeric viruses. The Baculovirus vector (a virus of insects) can infect mammalian cells, but it cannot replicate. This virus is not associated with disease in humans or animals.

The bursal disease-Marek's disease live vector vaccine is used to prevent infectious bursal disease in chickens (i.e., Gumboro disease), which can result in lack of coordination, watery diarrhea, and death in infected chickens; and Marek's disease (discussed previously). According to the CFIA report (2008b), the theoretical risk of recombination of the Marek's disease viral DNA and host DNA or other related viruses is low. Furthermore, any genetic changes would likely not be harmful and any effects from irregular gene expression would be minimized by the short life span of chickens. Risk of horizontal gene transfer is not higher or more severe than the risk from wild type (i.e., non-genetically modified) viruses. As discussed in the context of fowl laryngotacheitis Marek's disease vaccine, individuals working with chickens are at risk of being exposed to the recombinant viruses. However, exposure is not a significant health risk because Marek's disease does not readily infect mammals, and the Marek's disease viruses do not reproduce in vaccinated animals.

The live culture *Escherichia coli* (*E. coli*) vaccine consists of a live *E. coli* bacterial strain that has been inactivated by partial deletion of a gene required for growth. It is used to prevent disease caused by *E. coli* in poultry and other avian species. The CFIA (2008c) reported that the deletion of such a large part of the gene renders reversion back to pathogenicity unlikely. The vaccine cannot survive and persist in the target animal well; thus, the potential for the virus' genes to combine with the host's genes (termed "genetic recombination") is low. While there is a theoretical risk of horizontal gene transfer, the CFIA stated that any pathogenic bacteria created from gene transfer would not be more pathogenic than wild type strains and would be unable to persist in the environment. Waiting 21 days after inoculation for tissue residues of the vaccine to decrease (the "withdrawal period") before slaughtering animals reduces the likelihood of humans being exposed to the vaccine through meat from inoculated animals.

Additional Question #6. Can animals, or their offspring, be tested to determine GMO vaccine use?

One benefit of some GMO vaccines is the ability to track vaccinated animals. Traditional vaccines induce immune reactions that cannot be separated from immune reactions caused by natural exposure. However, marker vaccines (a type of subunit vaccine), which are made by deleting the genes of one or more microbial/viral proteins, allow the identification of vaccinated animals versus infected animals using a diagnostic test for a protein that is not present in the vaccine. Antibodies can be detected in both vaccinated and unvaccinated animals within a few weeks, including in milk from vaccinated animals (Radostits et al., 2000).

Additional Question #7. Benefits of GMO vaccines vs. non-GMO vaccines in the broadest sense, not just cost of production or time required from research to market.

GMO vaccines have potential advantages over conventional vaccines. For example, GMO vaccines are much more stable than conventional live vaccines during storage and handling. Modified live vaccines (MLVs; a common form of conventional vaccine) must be stored and handled properly or they risk loss of

potency (Radostits et al., 2000). The stability of vaccines is particularly important in areas where refrigeration is difficult (Roth and Henderson, 2001).

The virus in MLVs may become latent, resulting in generalized infection in immunized animals. This has been documented with conventional BHV-1 vaccine (Radostits et al., 2000). As discussed in Question 5, GMO vaccines may also become pathogenic if they mutate or recombine with other genes. However, as noted, the relative risk of recombination to virulence or ability to become virulent when administered to animals with suppressed immune systems is considered low for many GMO vaccines (Frey, 2007; Roth et and Henderson, 2001). In the case of BHV-1 vaccine, studies showed that the GMO BHV01 vaccine was both effective (with a hundred-fold reduction in viral replication and a shorter period of virus shedding), with reduced virulence and higher safety (Shams, 2005). This demonstrates that in some cases, GMO vaccines are safer than their traditional counterparts.

GMO vaccines have an advantage over conventional vaccines because they are assessed for risk *in vitro* prior to clinical trials, based on the known, deliberate genetic modifications. Conventional vaccines are produced using random mutagenesis of unknown target genes; without knowledge of the genetic background, safety testing is difficult. Most conventional vaccines were evaluated for safety through observations of adverse reactions and stability in clinical trials in experimental animals, without prior testing. There have been a number of conventional vaccines removed from the market after reverting to virulence or causing unintended effects. Furthermore, since conventional vaccines are not designed to be traced in the environment, environmental monitoring has historically not been done for these vaccines. GMO vaccines can be clearly distinguished from virulent pathogens and tracked (Frey, 2007).

It is also important to note that increased vaccination programs have resulted in lowered consumption of veterinary drugs. Livestock produced in accordance with organic standards can be given veterinary drugs if they are ill; however, any animal treated with antibiotics cannot be sold as organic. Because certain GMO vaccines are more efficacious than their conventional counterparts (e.g., DNA vaccines that induce cell-mediated immunity; conventional vaccines only induce humoral immunity) replacing them with the GMO vaccine would be expected to reduce disease in livestock, thereby reducing the need to use unapproved drugs on sick animals.

Additional Question #8. Does scale, or amount of use, impact type of vaccine developed (i.e., does the organic market warrant development of non-GMO vaccines)?

Economics appear to be the main driving force behind vaccine development. The goal of veterinary vaccines is to improve overall production for the primary producers, with cost-benefit analysis being the major consideration. Currently, vaccines represent about 23% of the global market of animal health products, with growth mainly due to biotechnological advances facilitating GMO vaccines (Meeusen et al., 2007). Based on the restrictions on antibiotic use in some farmers in the US and the European Union, the demand for efficacious vaccines will likely grow. According to Meeusen et al. (2007), the factor that determines the success of a new vaccine is successful commercialization and use in the field.

According to a USDA survey, livestock represented 10% of total sales of organic products (USDA, 2008). However, organic food sales made up only about 3% of total U.S. food sales in 2006 (AMRC, 2011). Livestock shares a relatively small percentage of the entire market for meat (organic and conventionally raised). For example, the market share of organic beef was 1.6% of the total market for meat (in terms of volume), based on a 2007 survey (AMRC, 2011). Organic poultry and eggs are more popular among consumers than organic beef products, although it is unclear what the market share is for organic poultry among all poultry sales (AMRC, 2011).

694 **References**

695 AMRC (Agricultural Marketing Resource Center). 2011.
696 http://www.agmrc.org/commodities__products/livestock/.
697
698 CAST (Council for Agricultural Science and Technology). 2008. Vaccine development using recombinant
699 DNA technology. Issue Paper 38. CAST, Ames, IA. Retrieved June 3, 2011 from
700 http://www.ca.uky.edu/poultryprofitability/Production_manual/Chapter20_Issues_affecting_the_US_br
701 oiler_industry/CAST_Biotechnology_paper7.pdf
702
703 CDC (Centers for Disease Control). 2011. Ingredients of vaccines – fact sheet. Retrieved June 3, 2011 from
704 http://www.cdc.gov/vaccines/vac-gen/additives.htm
705
706 CFIA (Canadian Food Inspection Agency). 2006. Environmental assessment for licensing in *Salmonella*
707 *typhurium* vaccine, live culture in Canada (Salmune). Accessed May 10, 2011 at http://epe.lac-
708 bac.gc.ca/100/206/301/cfia-acia/2011-09-
709 21/www.inspection.gc.ca/english/anima/vetbio/eaee/vbeasalmunee.shtml
710
711 CFIA (Canadian Food Inspection Agency). 2007. Environmental assessment for licensing in Canada porcine
712 cicrocvirus vaccine, type 1-type 2 chimera, killed virus. Accessed May 10, 2011 at
713 http://epe.lac-bac.gc.ca/100/206/301/cfia-acia/2011-09-
714 21/www.inspection.gc.ca/english/anima/vetbio/eaee/vbeachimerae.shtml
715
716 CFIA (Canadian Food Inspection Agency). 2008a. Environmental assessment for licensing porcine
717 circovirus vaccine, type 2, killed baculovirus vector in Canada. Accessed May 10, 2011 at http://epe.lac-
718 bac.gc.ca/100/206/301/cfia-acia/2011-09-
719 21/www.inspection.gc.ca/english/anima/vetbio/eaee/vbeapcve.shtml
720
721 CFIA (Canadian Food Inspection Agency). 2008b. Environmental assessment for licensing bursal disease-
722 Marek's disease vaccine, serotype 3, live Marek's disease vector in Canada. Accessed May 10, 2011 at
723 http://epe.lac-bac.gc.ca/100/206/301/cfia-acia/2011-09-
724 21/www.inspection.gc.ca/english/anima/vetbio/eaee/vbeamareke.shtml
725
726 CFIA (Canadian Food Inspection Agency). 2008c. Environmental assessment for licensing *Escherichia coli*
727 vaccine, live culture in Canada. Accessed May 10, 2011 at http://epe.lac-bac.gc.ca/100/206/301/cfia-
728 acia/2011-09-21/www.inspection.gc.ca/english/anima/vetbio/eaee/vbeaecolie.shtml
729
730 CFIA (Canadian Food Inspection Agency). 2010. Environmental assessment for the use of fowl
731 Laryngotracheitis-Marek's disease vaccine, serotype 3, live Marek's disease vector. Accessed March 3, 2011
732 at http://www.inspection.gc.ca/english/anima/vetbio/eaee/vbeafowllaryne.shtml#a5
733
734 CGSB (Canadian General Standards Board). 2009. Organic Production Systems Permitted Substances List.
735 Retrieved June 6, 2011 from http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/internet/bio-org/documents/032-
736 0311-2006-eng.pdf
737
738 Codex Alimentarius Commission. 1999. Guidelines for the production, processing, labeling, and marketing
739 of organically produced foods. Report GL 32-1999. 33 pp.
740
741 DHHS (Department of Health and Human Services). 2005. Influenza vaccine manufacturing: Issue brief.
742 Prepared by RTI International for DHHS. Department of Health and Human Services, Washington, DC.
743 Retrieved June 6, 2011 from http://aspe.hhs.gov/pic/fullreports/06/8476-2.doc
744
745 European Commission. 1999. Genetic and immunological safety of DNA vaccines. Retrieved March, 3, 2011
746 from http://ec.europa.eu/research/quality-of-life/gmo/08-vaccines/08-03-project.html
747

European Council for Classical Homeopathy (ECCH). 2008. Nosodes in homeopathy practice: An ECCH survey. Retrieved June 10, 2011 from http://www.scribd.com/doc/49160096/ECCH-Survey-2008-on-Nosodes-in-Homeopathic-Practice

Faras, A.J. and Muscoplat, C.C. 1985. The impact of genetic engineering on animal health and production. Journal of Animal Science 61:144-153.

Foley, P. 2011. Personal communication between Heather Simpson, ICF International, and Patricia Foley, DVM, PhD, Center for Veterinary Biologics. USDA, Animal and Plant Health Inspection Service (APHIS). [March 30-March 31, 2011].

Frey, J. 2007. Biological safety concepts of genetically modified live bacterial vaccines. Vaccine 25:5598–5605.

IFOAM (International Federation of Organic Agriculture Movements). 2010. The IFOAM norms. Retrieved June 6, 2011 from http://www.ifoam.org/about_ifoam/standards/norms.html

JMAFF (Japan Ministry of Agriculture, Forestry and Fisheries). 2005. Japanese Agricultural Standard for Organic Livestock Products. Retrieved June 6, 2011 from http://www.maff.go.jp/e/jas/specific/pdf/4.pdf

McCroy, L. and Barlow, J. (2006). Chapter 4: Evaluation of Homeopathic Nosodes for Mastitis and Calf Scours: Lessons from the Vermont Nosode Project. In: Morris, T.F.; and Keilty, J., eds. Alternative Health Practices for Livestock; pp 40–53. Retrieved March 3, 2011 from: http://books.google.com/books?id=9qgxVfI1Tk0C&pg=PA40&lpg=PA40&dq=nosodes+and+vaccinations+for+preventative+care+in+livestock&source=bl&ots=0FAvqktNdP&sig=ysUYHYT4WnZeBN5bVdWf72hTbAU&hl=en&ei=WpNuTePpCYP58AbIiL2ZDw&sa=X&oi=book_result&ct=result&resnum=9&ved=0CD8Q6AEwCA

MDH (Minnesota Department of Health). 2011. Retrieved June 6, 2011 from http://www.health.state.mn.us/divs/idepc/diseases/flu/hcp/vaccine/sh/vaxdisposal.html

Meeusen, E.N.T., Walker, J., Peters, A., Pastoret, P.-P., and Jungerson, G. 2007. Current status of veterinary vaccines. Clinical Microbiology Reviews 20(3):489–510.

Morton, D.B. 2007. Vaccines and animal welfare. Rev. Sci. Tech. Off. Int. Epiz., 2007, 26 (1), 157-163. Retrieved June 6, 2011 from http://www.oie.int/doc/ged/D4020.PDF

Morris, T.F.; and Keilty, M.T. 2006. Alternative health practices for livestock. Hoboken, NJ: John Wiley and Sons; 211 pp.

OMRI (Organic Materials Review Institute). 2011. Livestock Vaccines: Genetically Modified Organisms. OMRI Materials Review, Winter 2011.

Otto, R.B.D.; Crane, D.T.; and Bolgiano, B. 2007. A study of physico-chemical interactions between *Haemophilus influenzae* type b and meningococcus group C conjugate vaccines. Afri Health Sci 7(4): 190-196. Retrieved June 15, 2011 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074372/?tool=pubmed

Radostits, O.M., Arundel, J.H., and Gay, C.C. 2000. Veterinary medicine: a textbook of the diseases of cattle, sheep, pigs, goats and horses. Elsevier Health Sciences. Retrieved March 3, 2011 from http://books.google.com/books?id=Kqw2gCZFfhoC&pg=PT930&lpg=PT930&dq=genetically+modified+marker+vaccines&source=bl&ots=AX2ZqZIeCN&sig=XWqAEkYbYHeYN0qE5QtYUviZBYg&hl=en&ei=GBuTbznL8rQtwf0oJDrDg&sa=X&oi=book_result&ct=result&resnum=3&ved=0CCcQ6AEwAg#v=onepage&q=genetically%20modified%20marker%20vaccines&f=false

Roth, J.A., and Henderson, L.M. 2001. New technology for improved vaccine safety and efficacy. Vet Clin North Am Food Anim Pract 17(3):585-97, vii.

Shams, H. 2005. Recent developments in veterinary vaccinology. Vet J 170(3):289–99.

USDA (US Department of Agriculture's Center for Veterinary Biologics). 2011. Veterinary Biological Products. Retrieved May 12, 2011 from http://www.aphis.usda.gov/animal_health/vet_biologics/vb_licensed_products.shtml

USDA (US Department of Agriculture's Center for Veterinary Biologics). 2010. "USDA-APHIS-VS Center for Veterinary Biologics Licensed Biotechnology-Derived Products," document dated September 20, 2010, and provided by USDA to ICF International February 3, 2011.

USDA (US Department of Agriculture). 2008. 2008 Organic Production Survey. Retrieved May 2, 2011 from http://www.agcensus.usda.gov/Publications/2007/Online_Highlights/Fact_Sheets/organics.pdf

Traavik, T. 1999. An orphan in science: Environmental risks of genetically engineered vaccines. Research Report for DN 1999-6. Directorate for Nature Management. University of Tromsø, GENØK-Norwegian Institute of Gene Ecology, Tromsø, Norway.

Werner, C., Sobiraj, A, and Sundrum, A. 2010. Efficacy of homeopathic and antibiotic treatment strategies in cases of mild to moderate bovine clinical mastitis. J Dairy Res. 77(4):460–467.