

Excipients

Livestock

Identification of Substance

Chemical Names:

There are approximately 8,000 substances that qualify as excipients, far too many to list here individually. However, most chemicals used as excipients in organic livestock production are identified in the EAFUS¹ database, the List of Indirect Additives Used in Food Contact Substances², the Generally Recognized as Safe (GRAS) Notice Inventory³, or the FDA Inactive Ingredient Search for Approved Drug Products⁴.

According to the Animal and Plant Health Inspection Service (APHIS) (2014) excipients used in vaccines are largely classified as GRAS but a publicly available list of approved excipients is not available.

Otherwise, nonsynthetic substances may be used per §205.105 but a comprehensive list of those substances does not exist. Given the fact that APHIS does not publish a comprehensive list of excipients and there is no central list of all nonsynthetic substances, it is impossible to provide a complete list of all excipients eligible for organic production.

Other Name:

Formulants, Inactive ingredients, adjuvants

Trade Names:

N/A

CAS Numbers:

CAS Numbers can be identified in the EAFUS Database and the GRAS Notification Database.

¹ EAFUS (Everything Added to Food in the U.S.) is a database maintained by the U.S. Food and Drug Administration. The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS. Nevertheless, it contains only a partial list of all food ingredients that may in fact be lawfully added to food because under federal law some ingredients may be added to food under a GRAS determination made independently from the FDA. The separate FDA list contains many, but not all, of the substances subject to independent GRAS determinations. It also contains substances that were formally approved food additives but are now banned. These substances are delineated by DocType: BAN (FDA 2013). This database also contains the Color Additive Status List.

<http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm115326.htm>

² The List of Indirect Additives Used in Food Contact Substances is derived from substances appearing in 21 CFR Parts 175-178. Full context for the allowance of these materials can be found in the respective FDA regulations. Indirect food additives are food additives that come into contact with food as part of packaging, holding or processing, but are not intended to be added directly to, become a component of, or have a technical effect on the food. Indirect food additives mentioned in Title 21 of the U.S. Code of Federal Regulations (21CFR) used in food-contact articles include adhesives and components of coatings (Part 175), paper and paperboard components (Part 176), polymers (Part 177), and adjuvants and production aids (Part 178). Currently, additional indirect food additives are authorized through the food contact notification program. In addition, indirect food additives may be authorized through 21 CFR 170.39 (FDA 2011). <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=iaListing>

³ Substances that will be added to food are subject to premarket approval by FDA unless their use is generally recognized as safe (GRAS) by qualified experts. On April 17, 1997, FDA issued a proposed rule that would establish a notification procedure whereby any person may notify FDA of a determination by that person that a particular use of a substance is GRAS. Although the proposed notification procedure is not yet final, FDA started accepting GRAS notices in 1998. As described in the GRAS proposal, the agency is evaluating whether each submitted notice provides a sufficient basis for a GRAS determination, and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. Following this evaluation, FDA responds to the notifier by letter (FDA 2014).

<http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>

⁴ The Inactive Ingredient Database provides information on inactive ingredients present in FDA-approved drug products. This information can be used by industry as an aid in developing drug products (FDA 2013).

<http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm>

Other Codes:

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72**Summary of Use**

Excipients currently appear in the USDA National Organic Program (NOP) regulations at §205.603 only for use in the manufacture of drugs used to treat organic livestock when the excipient is: 1) identified by the FDA as Generally Recognized As Safe; 2) approved by the FDA as a food additive; or 3) included in the FDA review and approval of a New Animal Drug Application or New Drug Application. The National Organic Standards Board (NOSB) recommended in 2009 the addition of a fourth criterion for their allowance: “approved by APHIS” [for vaccines] (Animal and Plant Health Inspection Service; National Organic Standards Board 2009). Excipients are defined in §205.2 as “any ingredients that are intentionally added to livestock medications but do not exert therapeutic or diagnostic effects at the intended dosage, although they may act to improve product delivery (e.g., enhancing absorption or controlling release of the drug substance). Examples of such ingredients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents.”

Excipients are used in New Animal Drug Applications (NADAs) approved by the Food and Drug Administration (FDA), and in animal health care products that do not carry NADA registration. They are also used in New Drug Applications (NDAs) in drugs marketed for human consumption that may be administered to animals, such as aspirin.

Characterization of Substance**Composition of the Substance:**

Excipients are common in almost all therapeutic products for veterinary use, and in some cases the total amount of excipients used is greater than the active substances in the dose. They are derived from natural sources or are synthetically manufactured by chemicals, derived from genetically modified organisms, or manufactured by other means. They range from simple, whole food products, to highly characterized organic and inorganic molecules, to complex materials that are difficult to fully characterize chemically (Katdare and Chaubal 2006). Excipients can be added to the active substance individually or together in a formulated excipient package, depending on the drug (OMRI 2014). Excipients serve many functions but are typically comprised of suspending and viscosity-modifying agents, pH modifiers and buffering agents, preservatives, antioxidants, chelating agents, sequestrants, colorants, flavors, fillers, and diluents (Katdare and Chaubal 2006). While it is clear the functions that excipients serve, very few of them have been chemically described in any detail. Of the more than 8,000 food, drug, and cosmetic excipients available to conventional production, the CRC Handbook of Food, Drug, and Cosmetic Excipients (1992) only provides 77 detailed chemical monographs.

Source or Origin of the Substance:

Because excipients are manufactured for a wide variety of purposes, the source and origin is highly variable. They range from whole food products such as wheat middlings and yeast to synthetic food additives such as sodium benzoate and sodium lauryl sulfate. They may be agricultural, nonsynthetic or synthetic. Some are extracted or produced from plants, animals, minerals or microorganisms, and others are manufactured entirely from chemicals (OMRI 2014).

Properties of the Substance:

Table 1 describes the general physical and chemical properties of excipients based on the function they play in the drug:

Table 1: General physical and chemical properties of various categories of excipients ((Kemsley 2014; Katdare and Chaubal 2006; Carter 2006; Canovas-Barbaosa, et al. 2005; Bagul 2006; Leffingwell 2011; Cargill 2014; DOW Chemicals 2009).

Functional Category	Physical Properties	Chemical Properties	Examples
Filler or diluent	Good compression properties, strength and robustness when used in tablet form; allows for immediate release of the active ingredient; may be palatable and have good "mouth feel"	May be anhydrous or hydrated (liquid); ideally hygroscopic to be used with moisture sensitive active pharmaceutical ingredient (API)	Calcium phosphate, lactose, wheat middlings
Binder	Liquid, powder, or granule; good compression properties; may be sticky	Sugar or carbohydrate derivative	Molasses, starches, mannitol, sorbitol, xylitol
Disintegrant	Poor solubility, poor gel formation, good hydration capacity; good flow properties; non-reactive	Crosslinked cellulose and polymers or starch	Sodium starch glycolate, starch and starch derivatives
Lubricant	Low shear strength; non-toxic; insoluble in water	Hydrophobic, anti-static, consists of fatty acids	Magnesium stearate, glycerides
Glidant or anticaking agent	Insoluble, fine powders; strong water absorption	Mineral origin	Talc, colloidal silicon dioxide
Colorant	Dry (lakes) and liquid (dyes) forms; red, blue, green, yellow colors; non-reactive	Synthetic or nonsynthetic	Blue #1, Yellow #5, titanium dioxide
Capsule shell	Stable, resistant to capsule cross-linking; may be colored	Proteinaceous, colloidal gel when wet; brittle when dry	Gelatin, hypromellose
Coating agents	Liquid to solid application; hygroscopic; non-reactive	Carbohydrates or sugars; polysaccharides; waxes	Shellac, carnauba wax, alginates
Flavor or fragrance	May be solid or liquid; impart a characteristic taste or smell (floral, minty, fruity)	May be natural (derived from plant, animal, microorganism) or synthetic	Peppermint, berry
Release modifier	Gelling properties	Hydrosoluble; makes hydrophilic matrix system	Ethylcellulose, guar gum
pH modifiers	Solid or liquid forms; reactive; soluble in water	Acidic or basic in nature; organic or inorganic	Citric acid and its salts, phosphoric acid and its salts
Wetting or solubilizing agents	Typically solid or crystalline	Anionic, cationic, and amphoteric	Sodium lauryl sulfate, polysorbates
Preservatives	Low solubility; incompatible with many substances	Acid and non-acid types; reactive; bacteriostatic	Glycerin, benzyl alcohol, benzoate salts, antibiotics, sorbate salts.
Chelating or complexing agents	Liquid and crystalline forms	Molecule that forms several bonds to a metal ion; acidic and basic; both synthetic and nonsynthetic	Ethylenediaminetetraacetic acid salts (EDTA), cyclodextrins
Antioxidant	Fat soluble; liquid or	Both synthetic and	Ascorbic acid, butylated

	solid forms	nonsynthetic; mixtures of organic compounds; supply electrons or protons to free radicals	hydroxyanisole (BHA)
Sweetening agents	Exhibit sweetening properties at low concentrations; typically high caloric value; soluble in water; colorless, odorless	Carbohydrate-based; stable in acidic and basic conditions	Sucrose, saccharin

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Specific Uses of the Substance:

Excipients are used for a great number of applications in animal drug and health care products. However, there are broad categories (as listed in Table 1) that delineate the major reasons any given excipient is used. Following is a description of the function of each category listed in Table 1 (adapted from Kemsley 2014):

Filler or Diluent

Fillers and diluents increase the volume or weight of the formulated drug product. They also ensure that the active pharmaceutical ingredient dose is dispersed evenly across all other components.

Binder

Binders facilitate the agglomeration of powder into granules. They act as the “glue” that helps the pill or pellet to retain its form.

Disintegrant

Disintegrants promote rapid disintegration to allow the drug to dissolve at the desired rate. They are typically used in solid pill forms.

Lubricant

Lubricants reduce friction between particles in the drug, and between particles and manufacturing equipment. They also prevent sticking to packaging and pill packets. These are also often used in teat dips and/or bag balms to help disperse the active ingredient and to prevent chapping, thereby enhancing active ingredient absorption.

Glidants and anticaking agents

These ingredients promote powder flow and prevent caking or clumping. They also physically prevent the contamination of powders by microorganisms and moisture by helping to reduce accumulation and sticking in the corners or bottoms of packaging.

Colorants

Colorants produce a distinct color or appearance in the drug and can also prevent decay of light-sensitive ingredients. They are commonly used in drugs that are delivered via watering tanks to denote appropriate dispersion.

Capsules

Capsules contain the powder or liquid drug. They serve as delivery mechanisms in many ways, such as transport, packaging, and drug delivery. They are typically ingested along with the other ingredients.

Coating Agents

Coating agents are typically used with pills or boluses. They mask unpleasant tastes or odors, improve ingestion, protect ingredients from the environment, or modify the release of the active ingredient.

Flavor and fragrance

These improve palatability of the drug, especially when the other excipients and active ingredient are bitter or foul-tasting. They are also utilized in health care products to stimulate appetite.

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119 *pH modifiers*
120 These ingredients control pH to improve drug stability or to avoid irritation when consumed.
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122 *Wetting or solubilizing agents*
123 Wetting agents promote dissolution of insoluble ingredients. They help to disperse ingredients in water for
124 more even distribution of the active ingredient dose.
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126 *Preservatives*
127 Preservatives are used in liquid or semi-solid drugs to prevent the growth of bacteria, yeast, and mold.
128
129 *Chelating or complexing agents*
130 Chelators are used to bind metal ions in order to make them available to the animal in a biologically useful
131 form, or to prevent their interference with other processing steps or ingredients. They may also be used to
132 complex the active ingredient to make it shelf-stable, or to make it biologically active (e.g., iodine
133 complexes).
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135 *Antioxidants*
136 Antioxidants are added to reduce oxidation reactions that alter or decay ingredients. They scavenge free
137 radicals within the drug product. In some cases, they may serve as an antioxidant to the animal itself,
138 although this function would not qualify as an excipient.
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140 *Sweetening agents*
141 These types of ingredients are used almost exclusively for enhancing palatability of oral drug delivery.
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143 **Approved Legal Uses of the Substance:**

144 Excipients are legally permitted for use in the manufacture of vaccines and drugs⁵ for both human and
145 animal administration, but they must be reviewed as part of the vaccine or drug registration with the
146 respective federal regulatory agency. The FDA regulates the use of excipients in human and animal drugs,
147 while APHIS regulates excipients in vaccines and biologics (APHIS 2006). For new drug development
148 purposes, once an excipient has been approved in a NADA for a particular route of administration (e.g.,
149 binder), that excipient is not considered new and requires a less extensive review (FDA 2013). Each NADA
150 or NDA registered by the FDA is reviewed for the excipients as well as the active ingredient, and the
151 excipients are approved as part of the drug formula. Animal health care products that are not NADAs (not
152 registered with the FDA) also contain excipients. When a product on the market makes a claim on the label
153 as to the product's intended use to diagnose, cure, mitigate, treat, or prevent disease in animals, it comes
154 under the legal auspices of the FDA and is required to have a NADA. However, many health care products
155 on the market, including teat dips, electrolytes, bag balms, hoof baths, etc., do not carry registration and are
156 considered "illegally marketed drug products" by the FDA (FDA 2013). Those unregistered, illegally
157 marketed health care products are enforced by the FDA with "enforcement priorities" set by the agency
158 (FDA 2011). These enforcement priorities are based on safety risk to the general public. Many of the health
159 care products used in organic production are considered "low risk" and are of the last enforcement
160 priority. Some 'drug' products that are not registered NADAs but are used nonetheless in organic
161 production include teat dips, homeopathic treatments, hoof baths, mastitis control, and milk fever
162 treatments. All of these animal health care products commonly contain excipients (OMRI 2014).

⁵ The FDA defines the term 'drug' in 21 CFR 201 as "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement." (FDA 2014)

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164 In 2006 APHIS requested updated data from all licensees, permittees and applicants including a list of all
165 adjuvants and excipients in current use in biologics for food-producing animals, in order to expedite future
166 review and to update information on file (APHIS 2006). As mentioned previously, excipients in vaccines
167 and biologics are typically GRAS.

168 **Action of the Substance:**

169 Excipients act in many different ways depending on the intended form of the drug and particular active
170 ingredient. In general, most excipients are added for a particular function, as described earlier. In most
171 cases, the function also describes the mode of action, with some exceptions. For example, disintegrants act
172 to increase the rate of disintegration of the pill by expanding when in contact with moisture, thereby
173 breaking the cohesive pill into fragments. Various forms of starch act in this way and may be added for this
174 purpose (Augsberger, et al. 2006). Also, pH modifiers act by altering the pH (either up or down) of the
175 formula to promote the functionality of another drug component at a particular pH, and by stabilizing the
176 pH of the formula through buffering action. However, they can also prevent the functionality of active
177 drug ingredients delivered in animal water distribution systems by interacting with the active drug and
178 making it less effective (Dorr, et al. 2009). Wetting agents reduce surface tension of a liquid to allow it to
179 spread drops across a surface, increasing the spreading abilities of the liquid. These substances have strong
180 adhesive forces, attracting liquid to their molecules in different ways depending on the chemical nature of
181 the wetting agent (UC Davis 2014). Preservatives prevent the growth of unwanted microorganisms and
182 enzymes by altering the chemical composition of a product such that it is no longer a hospitable
183 environment, or by damaging the unwanted organisms' cell walls. Some substances that adjust the pH in
184 the formula also act as preservatives (e.g., citric acid) (Russel and Gould 2003).

185 **Combinations of the Substance:**

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187 Given the great variety of substances permitted as excipients in animal drugs and health care products, it is
188 impossible to list out all the combinations of these substances. In general, however, excipients are available
189 in individual forms and as commercially formulated products for addition to the active pharmaceutical
190 ingredient (API; OMRI 2014). Individual substances permitted as excipients may also have ancillary
191 substances such as stabilizers, preservatives, carriers, and anti-caking agents. Flavors, for example, may
192 contain carriers and preservatives to increase shelf-life. Minerals may contain anti-caking agents, while
193 lubricants might be a combination of oils and surfactants (OMRI 2014).

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195 Excipients are formulated with nonsynthetic substances and synthetics at §205.603(a) when those
196 substances are intended as the active ingredient in the animal drug. They are also added to injectable
197 vitamins and mineral solutions.

200 Status

201 **Historic Use:**

202 Prior to 2007, excipients did not appear in Section §205.603, and therefore synthetic forms were interpreted
203 to be prohibited for use in animal health care products and drugs. This led to some confusion among
204 producers and certification agencies as most health care products contain synthetic excipients. In 2002,
205 during the review of a number of synthetic active ingredients, the NOSB discovered that inactive
206 ingredients (excipients) in drugs posed a great problem for reviewing and approving livestock drugs. As a
207 result, the NOSB recommended at its October 2002 meeting adding excipients to §205.603. The NOP
208 consulted with the FDA, which recommended the current excipient annotation (AMS 2006). This
209 recommendation was not carried out until 2006 through a proposed rule (AMS 2006), and became effective
210 on December 13, 2007 (AMS 2007). Since 2007, the NOSB has recommended a number of actions, including
211 rule-making to amend the annotation to allow excipients as "approved by APHIS" in vaccines, and to
212 change "in the manufacture of drugs" to "in the manufacture of animal health care products" to address
213 the use of excipients in products that are not legal NADAs but nevertheless serve health care purposes
214 (NOSB 2009). The NOP stated they would execute rule-making to add the allowance for APHIS approved
215 excipients, but this rule-making has not happened at the the time of this report. Additionally, the NOP
216 found the term "animal health care products" to be vague and indicated that no action would be taken on
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218 this recommendation (NOP 2010). In 2009 the NOSB recommended allowing excipients in injectable
219 vitamins by adding to §205.603 injectable trace minerals, vitamins and electrolytes with the following
220 annotation: as nutritive supplements, formulated injectable supplements of trace minerals per
221 §205.603(d)(2), vitamins per §205.603(d)(3), and electrolytes per §205.603(a)(8), with excipients per
222 §205.603(f), in accordance with FDA and restricted to use by or on the order of a licensed veterinarian
223 (NOSB 2009). At the time of this report, this recommendation has not been carried out through rule-
224 making.

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226 Although synthetic excipients did not appear at §205.603 until 2007, they have been used in livestock drugs
227 and health care products with various interpretations by certification agencies and Material Review
228 Organizations (MROs) as to their allowance (NOSB 2009). Since their listing on §205.603, there has still
229 been some confusion among certification agencies about direct vs. indirect food additives, how those may
230 be used, and their compliance with the excipient annotation (since the annotation does not stipulate ‘direct’
231 food additives and only says “approved by the FDA as a *food additive*”) (emphasis added). Some
232 certification agencies permit the use of indirect food additives only in health care products that are
233 intended for external application (e.g., teat dips) while others do not permit them at all. Others permit
234 indirect food additives in all types of health care products, including oral and injectable formulas. Further,
235 despite the fact that injectable vitamins and minerals do not appear on the National List, certification
236 agencies appear to be consistently permitting their use with excipients as part of the formula. Finally, there
237 is some confusion about whether excipients appearing in the FDA Inactive Database for NADAs and
238 NDAs can be used in illegally marketed drugs as well, or if only NADAs and NDAs may contain
239 excipients from that particular database (Fernandez-Salvador 2014; personal experience).

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241 **Organic Foods Production Act, USDA Final Rule:**

242 Excipients do not specifically appear in OFPA, but Section 2110(f)(2)(A) requires that records be kept to
243 include amounts and sources of all medications administered. Excipients appear in the USDA organic
244 regulations Final Rule at §205.603 as follows: “only for use in the manufacture of drugs used to treat
245 organic livestock when the excipient is: 1) identified by the FDA as Generally Recognized As Safe;
246 2) approved by the FDA as a food additive; or 3) included in the FDA review and approval of a New Animal
247 Drug Application or New Drug Application.” The organic regulations at §205.238(a)(6) also requires the
248 administration of vaccines and other veterinary biologics to establish and maintain preventative livestock
249 health care practices, yet currently excipients approved by APHIS are not specifically included as
250 permitted synthetic excipients.

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252 **International**

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254 **Canada** - Canadian General Standards Board Permitted Substances List

255 [http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/programme-program/normes-standards/internet/bio-
256 org/permises-permitted-eng.html](http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/programme-program/normes-standards/internet/bio-
256 org/permises-permitted-eng.html)

257 Excipients are permitted under the Canadian Organic Standards. They appear in Table 5.3 as Formulants
258 (inerts, excipients), and can only be used in conjunction with substances listed in Table 5.3. The listing in
259 Table 5.3 does not specify any criteria for further compliance of such excipients.

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261 **CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing
262 of Organically Produced Foods (GL 32-1999)**

263 <ftp://ftp.fao.org/docrep/fao/005/Y2772e/Y2772e.pdf>

264 Excipients do not explicitly appear in the tables of permitted substances for organic livestock production.
265 However, the use of veterinary medicinal products is permitted under certain conditions according to
266 Health Care, Section 22, including chemical allopathic drugs. Excipients are not specifically mentioned in
267 this section.

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269 **European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008**

270 <http://www.organic-world.net/news-eu-regulation.html>

271 http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/l_189/l_18920070720en00010023.pdf

272 Excipients do not explicitly appear in the EU Council Regulation, EC No. 834/2007 or 889/2008. However,
 273 EC No. 889/2008 Section 4, Article 24 permits the use of chemically synthesized, allopathic veterinary
 274 treatments (including antibiotics) when phytotherapeutic, homeopathic products, trace elements and
 275 products listed in Annex V, part 3 and in Annex VI, part 1.1 are ineffective.

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 277 **Japan Agricultural Standard (JAS) for Organic Production**

278 <http://www.ams.usda.gov/nop/NOP/TradeIssues/JAS.html>

279 Excipients do not explicitly appear in the Japanese Agricultural Standard for Organic Livestock Production
 280 (Notification No. 1608). However, Article 4 allows the use of veterinary drugs including biological drugs
 281 and antibiotics. Article 3 defines three types of drugs and incorporates by reference other Japanese laws
 282 pertinent to animal health care and drugs.

283
 284 **International Federation of Organic Agriculture Movements (IFOAM)**

285 <http://www.ifoam.org/standard/norms/cover.html>

286 Excipients do not explicitly appear in the IFOAM NORM (Version 2014). However, Section 5.6 permits the
 287 use of chemical allopathic medical products when natural and alternative medicines and treatments are
 288 unlikely to be effective. Vaccines are also permitted in some cases. The norm also states that operators shall
 289 give preference to natural medicines, including homeopathy, Ayurvedic medicine and acupuncture.

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

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 293 **Evaluation Question #1: Indicate which category in OFPA that the substance falls under:** (A) Does the
 294 substance contain an active ingredient in any of the following categories: copper and sulfur
 295 compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated
 296 seed, vitamins and minerals; livestock parasiticides and medicines and production aids including
 297 netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is
 298 the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological
 299 concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert
 300 ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part
 301 180?

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 303 Excipients do not contain active ingredients that fall under any of the categories described in OFPA.
 304 Rather, they are inactive substances used in livestock medicines, internal parasiticides, and vaccines.

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

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 311 Due to the great variety of substances permitted as excipients, it is impossible to describe all prevalent
 312 manufacturing processes. However, most substances can be generally described as manufactured or
 313 formulated by a chemical process (e.g., potassium sorbate), or through chemical changes that occur when
 314 the substance is extracted from naturally occurring plant, animal and mineral sources (e.g., starch
 315 derivatives). Some substances may be considered nonsynthetic according to the USDA organic regulations
 316 (e.g., alginic acid). Nonsynthetic excipients that otherwise do not appear on any of the lists previously
 317 discussed are permitted per §205.105(a) unless they are specifically prohibited per §205.604. Some
 318 excipients may be derived from genetically modified organisms, such as starch from GMO corn, citric acid
 319 produced by genetically modified *Aspergillus niger* or GMO canola oil.

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 321 Below is a general description of possible manufacturing processes for functional categories as described in
 322 Table 1.

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 324 Table 2: Manufacturing processes by functional category.

Functional Category	
Filler or diluent	Common fillers and diluents include starch and starch derivatives, lactose

	<p>monohydrate, calcium phosphate, and microcrystalline cellulose and its salts (MCC). Starch is manufactured through water extraction, which may include the addition of a weak acid to facilitate the breakdown of the vegetable cells and release the starch (OMRI 2014). Starch derivatives (such as dextrin) are produced through chemical, mechanical, physical, or enzyme hydrolysis. Lactose monohydrate is a sugar derived from milk, and it is isolated by crystallization (DFE Pharma 2014). Calcium phosphate is either mined or is a byproduct of whey processing. It is deposited on the walls of the heater when the milk is heated (OMRI 2014). MCC is extracted from plant materials such as cotton or sorghum by sodium hydroxide delignification, followed by bleaching and acid hydrolysis. The microcrystalline cellulose is then reacted with metal ions to form salts (Ohwoavworhwa and Adelakun 2010).</p>
Binder	<p>Most binders are carbohydrates or alcohols such as maltodextrin, sorbitol, mannitol, erythritol or starches. The starch manufacturing process is described under 'fillers' above. Sugar alcohols are further processed from starch hydrolysates (dextrose) by hydrogenation (the chemical reaction between H₂ and another element). The resulting sugar alcohol depends on the "dextrose equivalent" in the starch hydrolysate (International Starch Institute 2012).</p>
Disintegrant	<p>The most common materials used as disintegrants are starches of various plant origins. Starch manufacture is described above under 'fillers'.</p>
Lubricant	<p>Magnesium stearate and stearic acid are the most frequently used lubricants in the pharmaceutical industry, although fatty acid esters (e.g., glyceride esters) are also commonly used in solid dose forms. Talc is another common lubricant when magnesium stearate is not effective. Stearic acid is manufactured from animal and vegetable fats via chemical, physical, or mechanical hydrolysis, and further fractionated (OMRI 2014). It can then be reacted with metal ions to form stearate salts, such as magnesium stearate. Glyceride esters are formed by esterifying glycerin with fatty acids. Talc is a naturally occurring mineral and is minimally processed (OMRI 2014).</p>
Glidant or anticaking agent	<p>Various calcium salts are used as anticaking agents (calcium phosphate, calcium silicate, calcium stearate) in addition to silicon dioxide, silicate salts, and corn starch. Manufacturing processes for calcium phosphate, stearates, and starches are described above. Silicon dioxide is produced from quartz stone and chemically processed to yield an isolated synthetic chemical. It can also be mined in the form of diatomaceous earth and further processed. Silicate salts may be naturally occurring in minerals, or chemically manufactured by reacting one or more minerals in solution (OMRI 2014).</p>
Colorant	<p>Two classes of colorants exist: those that are chemically manufactured and those that are extracted from natural substances such as plants and minerals. Artificial colors such as Blue #1 and Red#40 are manufactured with raw materials obtained from petroleum (Kobylewski and Jacobson 2010). Colors derived from natural substances may be extracted using synthetic solvents, water, alcohols, or other solvents (OMRI 2014).</p>
Capsule shell	<p>Capsules are generally made by dipping steel pins into liquid gelatin in successive turns to form gelatin films. Gelatin is manufactured by treating bone, pig skin or fish by-products (isinglass) with acid and lime, followed by hot water extractions, and then further filtered, evaporated, and sterilized (GMIA N.D.).</p>
Coating agents	<p>Gels and sticky substances are typically used as coating agents, including glucose syrup, maltodextrin, sodium alginate and carrageenan. Glucose syrup and maltodextrin are starch derivatives as described earlier, while sodium alginate and carrageenan are substances derived from seaweed. Seaweed is treated with an alkaline material, extracting alginic acid, which is reacted with a metal ion to produce alginate forms. Carrageenan is similarly manufactured but treated with precipitants to further purify it (Cargill 2014).</p>
Flavor or fragrance	<p>Flavors and fragrances are either chemically manufactured or extracted/isolated</p>

	from natural substances such as fruits, vegetables, yeasts, bark, roots, etc. When chemically manufactured, two or more substances are reacted to form a chemically unique substance lending the flavor/fragrance properties. Extracted flavors are typically manufactured via chemical solvents and/or water/steam/pressure distillation. Flavors and fragrances may come formulated with carriers, fillers, and preservatives (OMRI 2014).
Release modifier	Release modifiers are diverse substances that facilitate release of the active ingredient, and include ethylcellulose and guar gum. Ethylcellulose is a synthetic derivative of cellulose where the hydroxyl groups of the repeating glucose units are replaced with ethyl ether groups (Harke Group 2014). Guar gum is currently considered agricultural on §205.606.
pH modifiers	The pH modifiers are usually basic or acidic substances such as sulfuric, citric or hydrochloric acid, sodium or potassium hydroxide, or calcium carbonate. They can also be salts such as phosphate and citrate salts that are used as buffers. Most pH adjusters are synthetically manufactured by reacting minerals such as sulfur with air and water, or by reacting other chemicals such as hydrogen chloride in water. Hydroxides are manufactured by chemical synthesis. Some acids and bases are naturally occurring, such as mined calcium carbonate and fermented citric acid (OMRI 2014).
Wetting or solubilizing agents	Wetting agents are typically synthetic and are manufactured with chemicals derived from fatty acids and plant oils (peanut, coconut, olive). They may be esterified, reacted with amines, or they may be ethylene oxide adducts of fatty alcohols (Moorer and Sandefur 1976). Yucca extract is one of the few natural wetting agents available, and is water-extracted from yucca root (OMRI 2014).
Preservatives	Preservatives are typically synthetic and derived from chemicals. Common preservatives include benzoates and sorbates where a metal ion (potassium, sodium) is reacted with sorbic or benzoic acid to form the salt. Benzoic and sorbic acids are synthetic precursors to these reactions (Schmidl and Labuza 2000).
Chelating or complexing agents	There are natural and synthetic chelators. Natural chelators such as citric acid and gluconic acid are fermentation by-products. Synthetic chelators including EDTA are manufactured from chemicals (OMRI 2014).
Antioxidant	Antioxidants are mainly synthetic, but some are derived from natural materials. The most prominent antioxidants used are tocopherols, which are derived from plant oils but are processed in a way that renders them synthetic. Other antioxidants include ascorbic acid and ascorbate salts. Ascorbic acid is currently considered synthetic, and reaction with a metal ion would render the ascorbate salts synthetic as well (OMRI 2014).
Sweetening agents	Sweetening agents are derived from plant materials, either by direct extraction (sugar) or through starch hydrolysis (described earlier in 'fillers'). They may also include molasses, a natural sweetener derived from sugar beets or sugar cane. Synthetic sweeteners like saccharin are derived from chemical precursors.

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

As discussed earlier, excipients are manufactured in a great variety of ways that cannot all be summarized for this report. All types of chemical processes are used in the manufacture of these substances, although many excipients are from natural substances as well. Some of the chemical processes used to manufacture excipients include esterification, hydrogenation, hydrolysis, polymerization, reaction of two or more substances, etc. These processes take place in reactors, tanks, ion exchange columns, and other devices. Some substances are synthetically extracted from natural materials, such as flavors and fragrances. Solvents may include benzene, alcohol, or propylene glycol. Natural substances may be produced as fermentation by-products or from whole materials like mined minerals and food. According to Katdare and Chaubal (2006) most of the emerging excipients are categorized as “natural products (e.g. polymers

339 and derivatives), synthetic polymers, small molecules, natural products modified with synthetic polymers
340 (or vice versa), natural products modified by small molecules (or vice versa), and synthetic polymers
341 modified with small molecules (or vice versa).”

342

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

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346 Most of the available data about the accumulation of drugs in the environment focus on the active
347 ingredient rather than the excipients, even though they often make up the majority of the formula. It is
348 widely agreed in the scientific community that very little is known about the environmental fate of
349 pharmaceutical chemicals from agricultural sources (Diaz-Cruz and Barcelo 2008; Carlsson, et al. 2006;
350 Daughton 2001). Daughton (2001) summarizes the concern by noting that although active ingredients have
351 been known for decades to enter the environment via sewage,

352

353 “...a larger picture has emerged -- where it is evident that numerous drugs and personal care
354 products from a wide spectrum of therapeutic and consumer-use classes (many having potent
355 biochemical activity) can be inadvertently released to the environment (albeit yielding very
356 low concentrations). The routes of release include both direct (disposal and wastage from
357 external application) and indirect (excretion, washing, and swimming) -- primarily via treated
358 and untreated sewage effluent -- and also by terrestrial runoff (for example from confined
359 animal feeding operations - CAFOs - and excreta from medicated pets) and by wind-borne
360 drift of agriculturally applied antimicrobials to crops....Only limited subsets of the large
361 spectrum of commercial PPCPs⁶ have been documented in the environment so far. Many
362 therapeutic classes have not yet been surveyed for. The scope of the issue is ill-defined – the
363 numbers and types of PPCPs occurring in surface and ground waters across a large number of
364 watersheds and municipalities are only partly known. Few generalizations can be made. It is
365 reasonable to surmise, however, that the occurrence of PPCPs in waters is not a new
366 phenomenon – it has only become more widely evident in the last decade because continually
367 improving chemical analysis methodologies have lowered the limits of detection for a wide
368 array of xenobiotics in environmental matrices and have greatly expanded the ability to detect
369 polar compounds”.

370

371 As indicated by Daughton (2001), there are several ways that excipients may accumulate in the
372 environment: through manure and urine, through meat and milk products, and through contact with the
373 environment after a topical application (e.g., teat dips rubbing off on milking equipment). However,
374 current research is limited to their accumulation in manure, and the downstream effects of manure
375 application to soil.

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377 The primary way that excipients would accumulate in the environment is through the excretion of urine
378 and manure, especially when that excrement is collected and applied to organic crop land (Diaz-Cruz and
379 Barcelo 2008). Health care products administered orally or by injection are metabolized through the
380 various biological pathways, or may be released undigested or partially digested through manure and
381 urine. Kinney, et al. (2008) found that the application of swine manure containing anthropogenic waste
382 indicators (AWIs) to agricultural soil does result in transfer of these wastes to earthworms. Specifically,
383 swine manure containing AWIs from personal care products, biogenic sterols (natural steroids), and other
384 substances was applied to a conventional corn field and resulted in a detectable concentration of 19
385 different AWIs in the soil, and 21 AWIs in earthworms from the same site. While the authors did not make
386 conclusions about the effect of the wastes on earthworm health, they indicated that further research would
387 be needed to measure effects on organisms that consume earthworms (e.g., birds).

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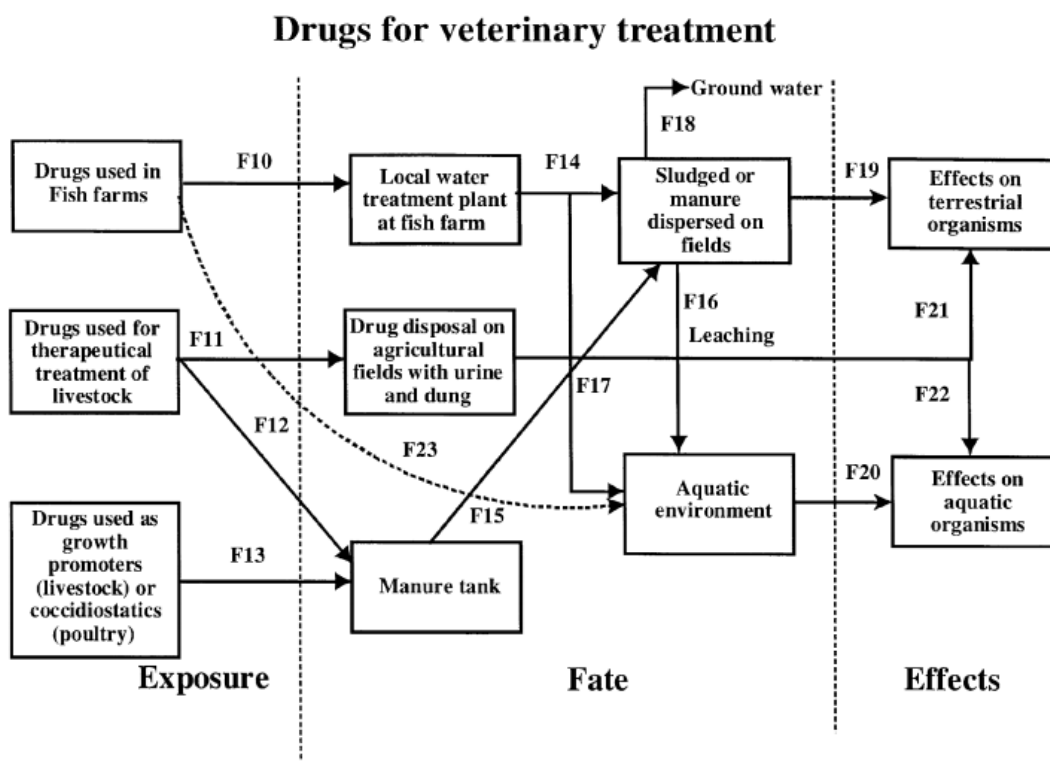
389 Another study assessed the potential environmental risks of five common excipients (chlorocresol,
390 docusate sodium, methylparaben, polysorbate 80, and sodium lauryl sulfate) to fresh surface water, fresh
391 water sediment, and soil exposed to sewage sludge (Carlsson, et al. 2006). Despite the fact that some of

⁶ PPCPs: Pharmaceutical and Personal Care Products

392 these substances are toxic to the aquatic environment if applied directly at low levels, the authors
 393 concluded that none of them posed a risk to the environment when used as pharmaceutical excipients due
 394 to the low levels of accumulation. However, the study also revealed there is a knowledge gap regarding the
 395 risk that pharmaceuticals pose to the environment, and more research is needed to provide better data
 396 about the substances themselves and their effects on the environment.

397
 398 **Evaluation Question #5:** Describe the toxicity and mode of action of the substance and of its
 399 breakdown products and any contaminants. Describe the persistence and areas of concentration in the
 400 environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).
 401

402 While the vast majority of excipients used in organic livestock health care products are GRAS or FDA
 403 approved food additives, they nonetheless are expected to persist in the environment in some cases, such
 404 as those described in Question #4. Part of the GRAS and food additive approval process is intended to
 405 show that the substance will be readily metabolized by the animal/human and excreted as harmless
 406 breakdown products (Alewynse 2009). However, some chemicals persist and accumulate in the
 407 environment as described earlier in Question #4. Daughton (2001) clearly summarizes the concern with
 408 pharmaceutical products in the environment and notes that very little is known about the environmental
 409 fate of these substances. It is known that the primary sources of PPCPs in the environment are sewage and
 410 domestic wastes, which for animal production include manure (Daughton 2001). Figure 1 describes the
 411 theoretical exposure, fate, and effects of veterinary drugs. Although it's believed that most pharmaceutical
 412 metabolites are broken down by soil organisms, the fact that manure is reapplied every year effectively
 413 replenishes the chemicals to the soil, thereby contributing to their concentration (Carlsson, et al. 2006).
 414 Question #4 details the limited data regarding some excipient concentrations in the environment.
 415



416
 417 Figure 1: Theoretical environmental exposure routes of drugs used for veterinary treatment (Jorgensen and
 418 Kalling-Sorenson 2000).
 419

420 **Evaluation Question #6:** Describe any environmental contamination that could result from the
 421 substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).
 422

423 When considering the environmental contamination posed during the manufacture, use, misuse, or
 424 disposal of excipients, it is important to note that the vast majority of the literature on this subject focuses

425 on the active ingredients rather than the excipients, or on both collectively as “pharmaceuticals,” and
426 makes no distinction between excipients and active ingredients. The reason that active ingredients seem to
427 be of more concern is because they have intrinsic biological activity that may cause adverse effects to the
428 terrestrial and aquatic environments. Unlike excipients, active ingredients are often designed to persist
429 through digestion and remain intact for maximum action in the body (Martin, et al. 2012). As discussed
430 earlier, besides excipients in NADAs, NDAs, and vaccines, most excipients used in organic animal health
431 care products are GRAS or FDA approved food additives and therefore assessed for human and
432 environmental safety by the FDA.
433

434 Considering the great variety of manufacturing processes described earlier for the various functional
435 classes of excipients, there are a number of environmental concerns in the manufacture of excipients. For
436 example, synthetic colorants are produced from petroleum products. The petroleum extraction business
437 has well-documented environmental effects such as groundwater contamination, natural resource
438 exploitation and depletion, spills into major water bodies, and contribution to greenhouse gas
439 concentration (Botkin 2010). Excipients may also be mined minerals or their derivatives. Mining is another
440 industry with well-documented environmental impacts, including exposure of toxic minerals to the
441 environment, heavy metal ground water leaching, effluent disposal into waterways, and brine disposal
442 (MIT 2014). Starches and their derivatives are common excipients, and there are some environmental
443 concerns from their manufacture. For example, starch facilities use a great deal of water and produce large
444 amounts of effluent that is high in organic content. If the effluent is not properly treated and disposed of, it
445 can result in ponds with strong odors (FAO 2000). According to the FAO (2000), communities consider
446 cassava starch production to significantly contribute to environmental damage and water deficit. Finally,
447 excipients may be derived from genetically modified soy, cotton, corn, canola, microorganisms, etc.
448 (GMOs). A review of recent studies on the environmental impact of GMOs indicate that their cultivation
449 leads to increased use of toxic pesticides and the development of herbicide resistant weeds (Benbrook 2009)
450

451 Solvents are commonly used in the production of excipients, especially flavors, fragrances, colors and
452 starches. Many organic solvents are carcinogenic and are regulated by the EPA as hazardous substances.
453 Some are point sources of air pollution and contribute to greenhouse gas concentrations (Bredenberg 2012).
454 In fact, the FDA recommends specific handling when using certain organic solvents in active and excipient
455 manufacture, including avoiding the use of highly toxic and environmental damaging solvents, and
456 monitoring the residual impurities in the final drug product (FDA 2011). Class 1 solvents (solvents to be
457 avoided) include benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, and 1,1,1-
458 trichloroethane.
459

460 Another concern in the manufacture of excipients relates to the complexity of the chemicals and the
461 inherent risk of adulterated products. It is well established that of the thousands of substances available as
462 excipients, most of them are not appropriately defined in monographs, and even fewer have assays
463 developed for proper identification. This has led to some issues with adulterated excipients, including
464 glycerin and propylene glycol adulterated with diethylene glycol, gelatin with melamine, heparin with
465 over-sulfated chondroitin sulfate, and milk (and its byproducts) adulterated with melamine (Moreton
466 2010).
467

468 Disposal of pharmaceuticals also contributes to the contamination of the environment, as they usually
469 make their way into the terrestrial and aquatic environments via the sewage system or manure. It is
470 common to dispose of unwanted or expired medication by pouring it down the sink or flushing it down
471 the toilet. Similarly, it is disposed of in the trash, which eventually makes its way into the groundwater via
472 landfill leachate (Kotchen, et al. 2009). Many studies have established that pharmaceutical compounds
473 contribute to soil and water contamination, especially via manure application, and these studies were
474 discussed previously (Daughton 2001; Carlsson, et al. 2006; Diaz-Cruz and Barcelo 2008; Kinney, et al. 2008;
475 Kotchen, et al. 2009).
476

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

480
481 Excipients are permitted in organic production only in combination with active health care ingredients that
482 are nonsynthetic or synthetic on §205.603 for health care purposes. Therefore, the main chemical
483 interactions that may occur are reactions between excipient substances, and between excipients and the
484 active ingredient. For instance, xanthan gum is anionic, and it is not compatible with cationic surfactants or
485 preservatives. In fact, excipients are added functionally to aid in API delivery, which may include
486 chemically interacting with the active ingredient to make it biologically available or shelf stable. Examples
487 of this particular interaction include complexing agents for iodine, flunixin, and chlorhexidine (OMRI
488 2014). There is some evidence that excipients can cause adverse effects when combined with certain active
489 ingredients or other excipients, and for this reason appropriate research and development is required to
490 ensure the intended effect and delivery of the active. For example, modified release excipients, if not
491 properly formulated, can lead to “dose dumping” or overdose, or can result in increased side effects
492 (Moreton 2010). The impurity profile of each ingredient should be compared to those used in drug
493 formulations, as impurities can be toxic in their own right or can interact with active ingredients. Even the
494 most commonly used magnesium stearate has had questions raised on the safety and toxicity of its
495 impurities (Katdare and Chaubal 2006). There is also evidence that certain excipients can cause prolonged
496 active ingredient excretion in milk. Specifically, Mercer, et al. (1970) found that aluminium monostearate as
497 a vehicle for antibiotics was consistently associated with prolonged excretion of the antibiotics in the milk.
498 No other study was found corroborating this phenomenon.

499
500 As described in Question #5, in some cases, excipients can inhibit drug delivery in water systems, thereby
501 contributing to greater concentrations of the active ingredient in wastewater. Dorr, et al. (2009) found that
502 pH adjusters used in the water delivery system affect the bioavailability of the active ingredient to animals,
503 and therefore care should be taken when considering water delivery systems.

504
505 **Evaluation Question #8: Describe any effects of the substance on biological or chemical interactions in**
506 **the agro-ecosystem, including physiological effects on soil organisms (including the salt index and**
507 **solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).**

508
509 As described earlier in Questions #4 and #5, there is evidence that pharmaceuticals and excipients transfer
510 to the agroecosystem via manure application. Kinney, et al. (2008) concluded that some substances can
511 transfer from manure to earthworms that consume it, and thereby will transfer up the trophic food chain to
512 birds. No conclusions were made about the effect on the earthworms, however. Similarly, Carlsson, et al.
513 (2006) found that some common excipients persist into the waterways, but they concluded that the levels
514 used in pharmaceuticals posed little risk to the environment. Overall, there is broad recognition among the
515 scientific community that many pharmaceutical chemicals are released into the environment but that little
516 is understood about their effects in what are currently small accumulations (Daughton 2001).

517
518 Although historically excipients were thought of as physiologically “inert” or inactive, some research
519 indicates that there is potential for excipients to exert physiological effects on the patient. For example,
520 certain lipid emulsion excipients have been found to affect intestine permeability and to inhibit certain
521 enzymes/transporters of key drug components, so that the active ingredient is not as well absorbed (Chen
522 2007). However, the excipients in question were part of a human drug formulation and were not intended
523 for animals. Antioxidants such as BHA (butylhydroxyanisol) appear to cause hyperplasia⁷ and carcinoma⁸
524 of the prestomach in rats at a dose of 20g/kg diet, while BHT (butyl hydroxytoluene) contributed to lesions
525 of the hepatic cells after chronic administration to laboratory animals. Organic mercurial salts are also
526 known to cause some adverse physiological effects in animals, including teratogenic⁹ effects (Pifferi and
527 Restani 2002). Certain phthalates, mainly dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP)
528 have been shown to be developmental and reproductive toxicants in laboratory animals. Effects include
529 decreased sperm counts in male animals and reduced fertility in female animals, skeletal abnormalities
530 such as fusion or absence of cervical vertebral arches, and fetal malformations such as cleft palate. Given

⁷ Hyperplasia is increased cell production in a normal tissue or organ. Hyperplasia may be a sign of abnormal or precancerous changes.

⁸ Carcinoma is another word for cancer.

⁹ Teratogenic: of, relating to, or causing developmental malformations.

531 the risk of these phthalates as excipients, and the existence of suitable alternatives, the Center for Drug
 532 Evaluation and Research has urged the pharmaceutical industry to avoid including them in drug and
 533 biologic formulas (Center for Drug Evaluation and Research 2012). Certain sweeteners such as dextrose,
 534 glycerin, lactose, mannitol, and sorbitol have side effects including nausea, vomiting, and laxative effects
 535 (Katdare and Chaubal 2006). Table 2 shows recent toxicology findings for a selection of excipients.
 536

537 Table 2: Examples of recently reported excipient toxicity (Katdare and Chaubal 2006)

Excipient	Toxicology Findings
Benzalkonium chloride (BZS) and potassium sorbate (PS)	Nasal lesions of inflammatory nature in rat.
Corn oil	Maternal toxicity (reduced body weight gain, food consumption, and renal pathology) and reduced pup viability in rat production toxicity study.
α - and β -cyclodextrins	Minor clinical pathology changes with urinary tract, liver and pancreas histopathology at 2000 mg/kg/day and above following continuous oral administration in rats; clinical pathology changes plus renal, urinary tract, lung, spleen and liver histopathology at 200 mg/kg/day and above with intravenous dosing in rats. Urinary tract changes and increased incidence of tumors in the pancreas and intestine seen in dietary carcinogenicity study in rats. Renal toxicity in rats from intraperitoneal dosing. Renal, cardio and lung toxicity in monkeys from intravenous administration.
Dibasic sodium phosphate	Nephrotoxicity in the form of proteinuria and glomerular calcification following intravenous (bolus) administration at 284 and 408 mg/kg/day for 14 days. These findings were not seen at 1 and 28 mg/kg/day.
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	Low level incidence of fetal clubfoot in older (1980s) rat teratology study following oral administration.
Menthol/peppermint oil	Evidence of genotoxicity in some in vitro assays.
Miglyol 812	Rats dosed orally with 10 mL/kg/day of 100% myglyol for 4 weeks showed soft and/or mucoid stools, reduced body weight gain, altered clinical pathology (decreased blood urea nitrogen, total protein, and globulins plus increased cholesterol and triglycerides), increased urine specific gravity, decreased thymus weight, and increased alveolar histiocytosis with focal interstitial inflammation; these changes reversed during a 4-week non-dose recovery period.
Polyethylene glycol-linked proteins	Marked renal cortical tubular vacuolation in mice and rats following parenteral administration.
Poloxamer 407	Hyperlipidemia (raised serum triglycerides and cholesterol) seen in rabbits injected with 137.5 mg/kg/day of 22% P-407 for up to 14 days. No effects were seen at lower doses of 5.5 and 27.5 mg/kg/day.
Propylene glycol	Maternal and reproductive toxicity in embryo-fetal studies in rabbits.
Polyvinylacetate phthalate	Gastrointestinal tract irritation in rats and dogs; embryo toxicity in rats and rabbits.
Stealth liposomes	Liposomal infusion reaction (hypoactivity, flushing, diarrhea, emesis, and decreased blood pressure seen following intravenous infusion in dogs).
L-tartaric acid	Nephrotoxicity seen with intravenous infusion in monkeys.

538
 539 **Evaluation Question #9:** Discuss and summarize findings on whether the use of the substance may be
 540 harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).
 541

542 As discussed in Questions #4 and #5, the primary mechanism through which excipients appear in the
 543 environment is via manure application to cropland. While it's widely agreed in the scientific community
 544 that pharmaceutical chemicals are ubiquitous in the environment, there is much less known about the
 545 actual effects, adverse or not, on the environment. Only a handful of studies have even identified the
 546 presence of specific excipients in the environment, while most studies rather focus on pharmaceuticals in
 547 general without making a distinction between active and excipient ingredients (Diaz-Cruz and Barcelo

2008; Carlsson, et al. 2006; Daughton 2001; Jorgensen and Kalling-Sorenson 2000). Since the majority of excipients used in organic livestock production are GRAS or FDA approved food additives, the potential for environmental and human health effects has been evaluated by the FDA as part of their legal status. No literature was found to show definitive harmful effects on the environment when excipients are used in animal health care products.

On the other hand, as discussed in Question 6, there are a number of environmental concerns related to the manufacture of excipients. Because of the great variety of substances permitted for use as excipients, it's expected that the manufacture of some substances would have detrimental environmental effects. Raw material extraction of petroleum products, solvents and mined minerals pose a number of negative environmental effects; the FDA has gone as far as recommend to the pharmaceutical industry to avoid certain solvents (e.g., benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethane, 1,1,1-trichloroethane) that pose exceptional environmental and human health risks (FDA 2011). Further processing of certain ingredients like starches and starch derivatives can lead to environmental degradation, air pollution, and exploitation of resources. A great number of excipients may be derived from GMOs and thus their use contributes to the cultivation of GMO soy, corn, cotton, etc. Excluded methods (GMOs) are prohibited in the production of organic products per §205.105(e) (except for vaccines provided they are approved in accordance with §205.600(a)) for the perceived negative environmental concerns surrounding them.

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the 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)).

Although there is no literature to indicate specific human health effects through the use of excipients in livestock health care products, there is significant literature to show that certain excipients can have detrimental and even lethal consequences when administered directly to human beings, especially infants. While the direct administration of drugs to humans is outside the scope of this report, it is worth noting that several cases of severe human health effects have led to greater focus on excipient safety in general. For example, a preparation of vitamin E intravenous injection for pre-term infants caused an unusual syndrome (E-ferol syndrome) and mortalities in low birth weight infants due the presence of widely used polysorbate 80 and polysorbate 20 preservatives (both GRAS) which inhibited the infants' response to the active ingredient (Alade, Brown and Paquet 1986). Cases such as these led researchers and regulatory agencies to focus greater efforts on identifying potential toxic risks of excipients, especially when combined with certain active ingredients. This is one reason the FDA assesses the safety of excipients as part of each NADA application, rather than individually in a separate program (FDA 2013). Now new excipients undergo a series of preclinical tests recommended by FDA and IPEC (International Pharmaceutical Excipients Council) that include acute oral and dermal toxicity, teratology, genotoxicity assays, and skin sensitization studies in rodents. These tests may be conducted on the excipient in combination with the active ingredient, or as a stand-alone ingredient (Katdare and Chaubal 2006).

Another way that excipients in livestock health care products may affect human health is through consumption of dairy and meat products of treated animals. In fact, the most likely route of exposure of humans to excipients in animal drugs is through residues in milk and meat. Most of the research on contamination has focused upon traces of antibiotics. But formulations specifically allowed in §205.603 can also appear in milk and meat. For instance, the FDA requires a withdrawal time of 4 days for flunixin and 35 days for injected ivermectin in non-lactating cattle. The flunixin withdrawal in lactating cattle is 36 hours. According to §205.603, withdrawal times for flunixin are at least twice that of the FDA. Presumably, both the active ingredient and the excipients are clear from commercial products by this time. For any traces left, excipients in organic formulations are mostly GRAS or approved food additives (National Dairy Farm Program 2011). There is a great deal of literature documenting chemical residues of various functions (pesticides, antibiotics) in cow's milk and human breast milk (by way of maternal diet), but no specific focus is given to excipients from animal drugs (WHO 2008). For example, the FDA published guidance for the veterinary industry to outline human microflora and fauna health considerations when evaluating the use of antimicrobial products in animal production. Specifically, "the FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most

603 significant pathway for human exposure to bacteria that have emerged or been selected as a consequence
604 of antimicrobial drug use in animals” (FDA 2003). Again, while the literature focuses on exposures to
605 active ingredients such as antibiotics, it serves as evidence that pharmaceuticals in fact carry through to
606 animal derived products. Phthalates were given specific attention, where the Center for Drug Evaluation
607 and Research (2012) advised the pharmaceutical industry to avoid their use as excipients due to potential
608 human health effects. However, since the majority of excipients used in organic livestock production are
609 GRAS or food additives, the FDA assessment would include human and animal effects of ingestion of such
610 ingredients, including their metabolism and breakdown pathways (Alewynse 2009).

611
612 As discussed previously, adulterated excipients pose some potential risk to human health, as most
613 prominently displayed in the 2007 case of melamine contaminated milk. Melamine is a synthetic
614 nitrogenous substance that was purposefully added to milk and other protein products to increase the
615 protein content. A number of children in China died from the adulteration, and as a result, the FDA
616 identified a partial list of excipients and active ingredients that may also be adulterated and need further
617 testing. These include: adenine, albumin, amino acids derived from casein protein hydrolysates,
618 ammonium salts, calcium pantothenate, caseinate or sodium caseinate, chlorophyllin copper complex
619 sodium, colloidal oatmeal, copovidon, crospovidone, dihydroxyaluminum aminoacetate, gelatin, glucagon,
620 guar gum, hyaluronidase, imidurea, lactose, melphalan, povidone, povidone-iodine, protamine sulfate,
621 protein hydrolysate powder for injection, and taurine (FDA 2009).

622
623 **Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be**
624 **used in place of a substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may**
625 **be used in place of the substance (7 U.S.C. § 6518 (m) (6)).**

626
627 As discussed previously, many excipients are available either exclusively in nonsynthetic form, or may
628 have nonsynthetic equivalents, while others are exclusively available in synthetic form. Many of the
629 sweeteners for example are nonsynthetic (sugar) or have nonsynthetic versions (maltodextrin).
630 Nonsynthetic colorants exist and are typically extracted from agricultural materials similar to those colors
631 appearing on §205.606. Disintegrants include starch materials, which are generally considered
632 nonsynthetic, although starch derivatives may undergo chemical processing such that they would no
633 longer be classified as nonsynthetic. Certain mineral chemicals may have natural mined analogues, but the
634 purity may be questionable for pharmaceutical purposes (Moreton 2010).

635
636 Despite the fact that nonsynthetic versions may exist for many excipients, their appropriateness as
637 alternatives must be carefully documented through research and development. As discussed earlier,
638 excipients are as important as the active ingredient for functionality and safety of the drug formulation,
639 and so great care is taken when selecting the appropriate substance. For example, a colorant used in a
640 bovine uterine flush to show that the entire dose is expelled must be potent enough to withstand normal
641 biological metabolism and absorption (OMRI 2014). There is evidence that even minute differences in
642 sources of identical substances can affect an excipient’s performance. Alvarez-Manceñido, et al. (2008)
643 found that three sources of konjac glucomannan from Europe, the USA, and Japan behaved differently
644 when combined with xanthan gum, despite the fact that these places all have excipient harmonization
645 policies. Specifically, the authors found that sources from Japan and Europe interacted with xanthan gum
646 to form gels, while the American variety only formed a visous solution. The different gelling capabilities
647 were attributed to the degree of acetylation in the konjac, a detail that would only become evident during
648 formulation development rather than from a specification sheet for synthetic or nonsynthetic versions of
649 the same substance.

650
651 **Evaluation Question #12: Describe any alternative practices that would make the use of the substance**
652 **unnecessary (7 U.S.C. § 6518 (m) (6)).**

653
654 Excipients in organic livestock production are widespread and are necessary in health care products
655 ranging from preventative herbal products such as bag balms to registered drugs such as flunixin and
656 ivermectin. Although it is common to assume producers can avoid the use of excipients by resorting to the
657 use of natural or nonsynthetic health care products, these too depend on excipients to deliver the active

658 ingredients, provide shelf stability, and ensure safety of the formulation. Therefore, there are no realistic
659 alternatives to using excipients when formulating livestock health care products.

660
661 One alternative to the use of excipients is through reducing or eliminating the need for animal health care
662 products. Although the organic livestock producer must establish and maintain preventive livestock health
663 care practices according to §205.238, which include a number of management techniques such as
664 appropriate housing, reduction of stress, and access to pasture, these management techniques are typically
665 not enough to prevent all illnesses and eliminate the need for health care products. Further, the use of
666 vaccines and biologics as part of the preventative management plan is required per §205.238, and vaccines
667 necessarily include excipients. Therefore, this is not a realistic alternative to the use of excipients either.

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