United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/petitioned-substances

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Injectable Nutritive Supplements

Livestock

Identification

Chemical names:

We identified 28 vitamins, minerals, and electrolytes that are used for animal health and align with the National List annotation at 7 CFR 205.603(a)(21) (see *Table 1*). These active ingredients were identified based on their inclusion in either a current FDA approved injectable formulation or inclusion in data collected from a small group of certifiers (FDA Center for Veterinary Medicine, 2025a; OMRI, personal communication, October 3, 2025). This technical report discusses not only the active ingredients, but also formulations of these injectable vitamins, minerals, and electrolytes.

Table 1: Common active ingredients in injectable supplements

Common name	Chemical name	CAS number	EC number
Calcium borogluconate	Calcium bis((2R,3R)-2,3-dihydroxy-3-[(4S,5R)-2-hydroxy-5-(hydroxymethyl)-1,3,2-dioxaborolan-4-yl] propanoate)	5743-34-0	227-264-1
Calcium chloride, dihydrate	Calcium dichloride	10043-52-4	233-140-8
Calcium gluconate	Calcium bis((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoate)	299-28-5	206-075-8
Calcium hypophosphite	Calcium phosphinate	7789-79-9	232-190-8
Calcium propionate	Calcium propanoate	4075-81-4	223-795-8
Calcium sulfate	Calcium sulfate	7778-18-9	231-900-3
Copper carbonate	Copper carbonate	1184-64-1	231-325-8
Ferric oxide	Oxo(oxoferriooxy)iron	1309-37-1	215-168-2
Iron dextran	Iron dextran	9004-66-4	618-390-1
Magnesium gluconate	Magnesium; bis((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate); dihydrate	59625-89-7	890-149-5
Potassium chloride	Potassium chloride	7447-40-7	231-211-8
Sodium chloride	Sodium chloride	7647-14-5	231-598-3
Sodium hypophosphite	Sodium phosphinate	7681-53-0	231-669-9
Sodium lactate	Sodium 2-hydroxypropanoate	72-17-3	206-231-5
Sodium selenite	Disodium; selenite	10102-18-8 (anhydrous); 26970-82-1 (hydrate)	233-267-9
Vitamin A (retinol)	(2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol	68-26-8	200-683-7 (retinol); 204-844-2 (retinol acetate); 234-328-2 (vitamin A)
Vitamin B_1 (thiamine)	5-(2-Hydroxyethyl)-3-[(6-imino-2-methyl-1,6-dihydro-5-pyrimidinyl) methyl]-4-methyl-1,3-thiazol-3-ium chloride	59-43-8	200-425-3
Vitamin B_2 (riboflavin)	7,8-dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl] benzo[g]pteridine-2,4-dione	83-88-5	201-507-1
Vitamin B_3 (niacin; nicotinic acid; nicotinamide)	Pyridine-3-carboxylic acid (niacin); pyridine-3-carboxamide (nicotinamide)	59-67-6 (nicotinic acid); 98-92-0 (nicotinomide)	200-441-0 (nicotinic acid); 200-659-6 (nicotinamide)
Vitamin B_5 (pantothenic acid; d-pantothenic acid)	3-[[(2R)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino]propanoic acid	79-83-4	201-229-0
Vitamin B_6 (pyridoxine)	4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol	65-23-6	200-603-0
Vitamin B_7 (biotin)	5-[(3aS,4S,6aR)-2-oxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-d] imidazol-4-yl] pentanoic acid	58-85-5	200-399-3
Vitamin B_{12} (cobalamin; cyanocobalamin)	Cobalt(3+); [(2R,3S,4R,5S)-5-(5,6-dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl] [(2R)-1-[3-[(1R,2R,3R,5Z,7S,10Z,12S,13S,15Z,17S,18S,19R)-2,13,18-tris(2-amino-2-oxoethyl)-7,12,17-tris(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1H-corrin-24-id-3-yl]propanoylamino]propan-2-yl] phosphate; cyanide	13408-78-1	236-500-2
Vitamin C (ascorbic acid; l-ascorbic acid)	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one	50-81-7	200-06-23
Vitamin D_2 (ergocalciferol)	(3S,5Z,7E,20R,22E,24R)-9,10-Secoergosta-5,7,10,22-tetraen-3-ol	50-14-6	200-014-9
Vitamin D_3 (cholecalciferol)	(3S,5Z,7E)-9,10-Secocholesta-5,7,10-trien-3-ol	67-97-0	200-673-2

Common name	Chemical name	CAS number	EC number
Vitamin E (tocopherol; α-tocopherol; alpha-tocopherol)	(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	59-02-9	233-466-0
Vitamin K_1 (phytonadione)	2-methyl-3-[(*E*)-3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione	84-80-0	201-564-2
Zinc oxide	Zinc oxygen (2-)	1314-13-2	215-222-5

Trade names:

Individual injectable supplements are not always sold under a specific trade name. They are commercialized as formulations containing mixtures of vitamins and minerals (NOP, 2015). One or more vitamins may be deficient in particular situations and for this reason they are commonly formulated together in injectable preparations. Common formulations are identified and discussed in greater detail later in the report (see *Combinations of the Substance* below).

Summary

This limited scope technical report provides information to the National Organic Standards Board (NOSB) to support the sunset review of the injectable versions of nutritive supplements, listed at § 205.603(a)(21).

Information requested by the NOSB related to injectable supplements in livestock:

The NOSB requested information on the following:

- *Focus Question 1: Are there any unique attributes to the injectable formulas of these substances relevant to National List criteria that NOSB should consider in its sunset review?*
- *Focus Question 2: Do any injectable formulas include excipients allowed via 205.603(f) that are not found in the non-injectable versions of electrolytes, vitamins, and minerals? If yes, please describe.*

There are numerous nutritive supplements encompassed by the entry at § 205.603(a)(21). In this report, we include information found for both complete formulations, and, in cases where we are unable to identify complete formulations, on specific ingredients known to appear in formulations. However, to comprehensively review each vitamin and mineral and proprietary formulation is not possible due to the lack of information available to the public, and the scale of such an undertaking within a single report.

To address *Focus Question 1*, we investigated formulation attributes unique to the injectable form of these supplements in the context of the following sections:

- *Specific Uses of the Substance*
- *Evaluation Question #1(D) and (E)*
- *Evaluation Question #6*
- *Evaluation Question #8*
- *Evaluation Question #9*
- *Evaluation Question #10*

To address *Focus Question 2*, we investigated the injectable formulations and compared them to their oral formulation counterparts in the context of the following sections:

- Combinations of the Substance
- Specific Uses of the Substance

Additionally, we provide background and composition information to supplement the questions posed by the NOSB.

Background

USDA organic regulations:

The regulatory landscape for injectable supplements used for organic livestock healthcare is complex. In 2006, the NOP stated that six substances, including two injectable supplements (calcium borogluconate and calcium propionate), could not be added to the National List as medical treatments (proposed rule, July 17, 2006, 71 FR 40624). The explanation provided by NOP at the time was that these materials were not FDA-approved and do not qualify for extra-label use by veterinarians under the Animal Medical Drug Use Clarification Act (AMDUCA) provisions (83 FR 66559).[1] Calcium borogluconate and calcium propionate are electrolytes commercially available in injectable forms.

[1] Extra-label use describes any use of an FDA-approved drug that differs from instructions on the approved product label.

Injectable supplements were petitioned for addition to the National List in 2009 (NOSB, 2009). Although the related National List entry was not added until 2019, the NOSB made a recommendation in 2009. In that recommendation, the NOSB acknowledged that reviewing every vitamin and mineral, as well as proprietary injectable formulations, is not feasible. Furthermore, due to the numerous formulations available for these materials, farmers and veterinarians are likely to reach for the most readily available product (NOSB, 2009). Taking this 2009 observation into account, this report aims to either confirm what the NOSB Livestock Subcommittee previously recognized or, when possible, report on these different formulations.

In January 2019, nutritive supplements (injectable supplements) were added to the National List for use in organic livestock production (83 FR 66559). Before this, these materials were allowed under the USDA organic regulations only as part of the total feed ration, either as feed additives [vitamins and minerals per 7 CFR 205.603(d)] or as medical treatments [electrolytes without antibiotics per § 205.603(a)]. Before the publication of the rule, effective January 28, 2019, the NOP conferred again with the FDA on the proposed additions and amendments to § 205.603. At that time, the FDA indicated that its process involved reviewing formulated products for approval as medical treatments. The FDA stated that it does not review generic materials for medical treatment approval, as included on the National List. Therefore, individual substances cited on the National List would not be reviewed as medical treatments under the FDA process. Based on this consultation, NOP believed that calcium borogluconate and calcium propionate were not in conflict with FDA regulations (83 FR 66559). Calcium borogluconate and calcium propionate were added as individual entries to the National List at § 205.603(a), also in January 2019 (83 FR 66559). The NOSB continued to recommend renewing both substances in 2021 (NOSB, 2021). These entries on the National List are separate from both the electrolytes and injectable supplements entries.

FDA oversight:

The National List entry at 7 CFR 205.603(a)(21) indicates nutritive supplements-injectable supplements must be used in accordance with FDA and restricted to use by or on the order of a licensed veterinarian. The FDA oversees products that are either "food" or "drug substances" depending on their intended use (FDA Center for Veterinary Medicine, 2025d). The term "drug substance" pertains to any material intended to diagnose, treat, or prevent disease in animals or to affect the structure or any function of the animal's body (FDA, 2024b). To legally market an animal drug substance for food-producing animals, a drug company must get the drug product approved or conditionally approved by FDA (FDA Center for Veterinary Medicine, 2020). Each designation has different requirements, but both lead to legal marketing status and involve a pre-market review by the FDA. The pre-market review assesses if the drug is safe and effective for a specific use in a specific animal species. If the drug is for use in food-producing animals, the manufacturer must also demonstrate that food made from animals treated with the drug is safe for human consumption. The FDA also determines if veterinary oversight is required for the safe and effective use of a drug (FDA Center for Veterinary Medicine, 2024b). If the agency determines that adequate "directions for use" can be written on the drug's label in such a way that a non-veterinarian can use the drug safely and effectively, then the drug company can market the animal drug as over-the-counter (OTC). If not, then the drug company must market the animal drug as either prescription (Rx) or veterinary feed directive (VFD) (FDA Center for Veterinary Medicine, 2024b).

All FDA approved animal drugs have a New Animal Drug Application (NADA) number, or for generic animal drugs, an Abbreviated New Animal Drug Application (ANADA) number (FDA Center for Veterinary Medicine, 2024e). Most FDA-approved and conditionally approved animal drugs are included in the online publication, *Approved Animal Drug Products*, called the *Green Book*. There are 15 injectable drug products currently listed in the *Green Book* approved for use in at least one life stage of food animal species that also have active ingredients that are vitamins, minerals, or electrolytes (see *Table 3*) (FDA Center for Veterinary Medicine, 2025a). Drug manufacturers are required to include the two segment, six-digit application number on most label components for currently approved and marketed animal drugs (FDA Center for Veterinary Medicine, 2024e).

- If the number is less than 200-000, the animal drug is a brand name drug with an approved NADA.
- A number over 200-000 indicates the animal drug is a generic drug with an approved ANADA.

Rather than the full NADA process that a brand name animal drug goes through, a generic animal drug goes through the ANADA process. This process does not require the drug company to conduct new safety and effectiveness studies with the generic animal drug. However, the FDA does require a generic drug to demonstrate the same quality, performance, and intended uses as the brand name drug (FDA Center for Veterinary Medicine, 2024e).

Conditionally approved animal drugs are also available for use in a minor species, or in a major species under special circumstances (FDA Center for Veterinary Medicine, 2024b). FDA classifies horses, dogs, cats, cattle, pigs, chickens, and turkeys as the seven major species. All other animals, such as sheep, goats, and hamsters, are minor species.

There are also large volume parenterals (injections). These are animal drug products commonly administered by veterinarians as large volume injections in volumes of 100 ml to 5,000 ml to provide fluid therapy to dehydrated

animals (FDA Center for Veterinary Medicine, 2019b). Large volume parenteral products may contain vitamins, minerals, and electrolytes. These products may also be considered new animal drugs and considered unsafe and adulterated if marketed in the absence of an approved new animal drug application. However, in a compliance policy guide published in 2019, the FDA noted that they usually do not take action against the manufacturers of these large volume parenteral products, as long as, the drug products meet all of the following criteria (FDA Center for Veterinary Medicine, 2019b):

- Sterile.
- Free of preservatives, unless the product is the subject of an approved NADA that permits use of the preservative in that particular product.
- Supplied in appropriate volumes to ensure one-time, single-patient use.
- Labeled to indicate that:
    - they contain no preservatives.
    - they must be used promptly upon opening.
    - any unused portion should be discarded.
- Labeled to indicate the concentration of individual ingredients and physiological parameters of the solution.
- Labeled with the U.S. Federal prescription legend: "CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian."
- Labeled in compliance with other applicable requirements in the Federal Food, Drug, and Cosmetic (FD&C) Act and its implementing regulations.
- Manufactured in accordance with current Good Manufacturing Practices.
- Manufactured by an establishment that is registered with FDA (21 CFR 510).
- Listed with FDA (21 CFR 510).
- Not adulterated.
- Not misbranded.

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) also permits veterinarians to prescribe extra-label uses of certain approved new animal drugs and approved human drugs for animals under certain conditions (21 CFR 530). Veterinarians cannot prescribe extra-label uses of conditionally approved and indexed animal drugs (FDA Center for Veterinary Medicine, 2023). Under AMDUCA, any extra-label use of an approved new animal or human drug must be by or on the lawful order of a veterinarian within the context of a veterinarian-client-patient relationship (VCPR) (FDA Center for Veterinary Medicine, 2024d). There are also additional specific conditions that must be met for extra-label use of approved animal and approved human drugs in food-producing animals.

An indexed animal drug is a drug on FDA's *Index of Legally Marketed Unapproved New Animal Drugs for Minor Species*, referred to simply as "the Index" (FDA Center for Veterinary Medicine, 2024b). These materials are unapproved, but a drug listed on the Index has legal marketing status. However, the use of these drugs in food animals is restricted to early, non-food life stages of a food-producing minor species, and only when the manufacturer can demonstrate the drug product meets human food safety standards (21 CFR 516). There are no indexed animal drugs marketed for use in early, non-food life stages of a food-producing minor species currently (FDA Center for Veterinary Medicine, 2025c).

A drug manufacturer can legally market a new animal drug product once the FDA approves, conditionally approves, or indexes it (FDA Center for Veterinary Medicine, 2020). The presence of a National Drug Code (NDC) number on an animal drug's label does not indicate the drug is legally marketed (FDA Center for Veterinary Medicine, 2024e). Under federal law, all drug manufacturers must register with FDA and give the agency a list of their marketed drugs. This requirement for drug manufacturers to "register and drug list" with FDA applies to all marketed drugs, including unapproved ones. FDA assigns a unique three-segment NDC number to each drug listed by a registered drug manufacturer, regardless of whether it's legally marketed or not, to indicate the drug is in commercial distribution (FDA Center for Veterinary Medicine, 2024e).

Characterization

Composition of the Substance:

Electrolytes and minerals

Minerals are inorganic (*i.e.,* not containing carbon) compounds essential to the bodily functions of animals (Cherian, 2019a). Minerals support many metabolic processes, including cell membrane function, immunity, and growth. There are 21 essential minerals that animals need to consume through their diet (Cherian, 2019a).

Minerals are classified as either macro- or micro-. These terms indicate the relative amounts of them required in an animal's diet. Animals require macrominerals in large quantities (> 0.01% of the diet). These include (Cherian, 2019a):

- calcium
- phosphorus
- magnesium
- sulfur
- sodium
- potassium
- chloride

Microminerals are required in trace amounts (< 0.01% of the diet). These include (Cherian, 2019a):

- manganese
- zinc
- iron
- copper
- selenium

Unlike the macrominerals list, this list of microminerals is not comprehensive. Of the trace minerals commonly included in dietary formulations, we highlight minerals in this report that organic operations also commonly use as injectable supplements (OMRI, personal communication, October 3, 2025). These are trace minerals associated with urgent health issues that may arise as a result of dietary deficiencies (see *Specific Uses of the Substance*).

Electrolytes are dissolved ions in solution that carry a charge (Chow, 2021). Electrolytes in animal bodies regulate the flow of water molecules and the electrical charge across cell membranes (Barton & Kirby, 2016). There is some overlap between minerals and electrolytes. The following minerals are also electrolytes that play a critical role in maintaining normal cellular functions (Barton & Kirby, 2016):

- sodium
- potassium
- chloride
- calcium
- magnesium
- phosphorus

Vitamins

Vitamins are organic compounds that play essential roles in the functioning of enzyme systems (AAFCO, 2024). These roles are crucial for regulating metabolism. Animals obtain most of their vitamins through their food (Cherian, 2019b). They can also obtain certain vitamins through specific processes (Cherian, 2019b). For example, B vitamins can be synthesized by the rumen microbes in cattle, sheep, and goats.

Vitamins are classified based on their solubility, as fat- or water-soluble vitamins (Cherian, 2019b). The fat-soluble vitamins are vitamin A, vitamin D, vitamin E, and vitamin K. The water-soluble vitamins include members of the B-complex group and vitamin C.

Combinations of the Substance:

There are several common injectable supplements. These may be formulated with multiple active ingredients and technical additives in various combinations (see *Table 2*) (FDA Center for Veterinary Medicine, 2025a; OMRI, personal communication, October 3, 2025). In this report, the term "technical additive" refers to any formulation ingredients that are not the active component of the supplement. By using this term, we aim to alleviate the discrepancies between the language in the organic standards and allow, where applicable, effective comparison of injectable formulations to their oral formulation counterparts. There are no allowances for excipients in any other oral vitamin or mineral formulations. According to NOP Guidance 5030 *Evaluating Allowed Ingredients and Sources of Vitamins and Minerals For Organic Livestock Feed* at item 4.2.3(c), vitamins and minerals may contain other minor ingredients that are considered part of the approved vitamin or mineral source (NOP, 2013a). However, all of these terms describe substances added to the active ingredients during the manufacture of the supplements to aid the production of a commercially viable product.

Preservatives and pH buffer solutions are common technical additives included in injectable formulations (Merck & Co., Inc., 2024; OMRI, personal communication, October 3, 2025). Buffers are necessary to maintain both the solubility of the active ingredient and the stability of the product (Merck & Co., Inc., 2024). Manufacturers balance the relative concentration of dissolved materials within the formulation by adding tonicity-adjusting agents (*e.g.,* salts) as needed. Injecting solutions with an improper salt balance can cause damage to red blood cells.

Sterile water for injection is the most widely used solvent for injectable supplements (Robinson et al., 2024). However, a non-water solvent or a mixed combination of water and non-water solvent may be necessary to stabilize ingredients that readily react with water, or to improve solubility. Manufacturers may also use inert gases (*e.g.,* nitrogen or carbon dioxide) to replace the air in packaged solutions. The addition of these gases may also slow the deterioration of oxygen-sensitive supplements (Robinson et al., 2024).

Table 2: Common combinations of injectable supplements

Primary active ingredient	Primary active ingredient forms	Additional active ingredients	Additional active ingredients forms	Technical additives	Generic names	Trade names
Calcium (with other electrolytes)	Calcium borogluconate; calcium chloride dihydrate; calcium gluconate monohydrate; calcium sulfate	Magnesium, phosphorus, and potassium	Magnesium borogluconate; magnesium gluconate dihydrate; calcium hypophosphite; potassium chloride; sodium hypophosphite monohydrate; sodium lactate	Boric acid; dextrose (D-glucose)	Calcium borogluconate; Calcium gluconate; CMPK solution; Ringer's lactated solution	Calcicure; Cal Dex CMPK Injection; Calcium Gluconate 23%; Cal-Phos#2 with Potassium; VetOne CMPK Solution
Electrolytes (without calcium)	Sodium chloride	None	---	None	Hypertonic saline 7.2%	Vetivex® Hypertonic Saline Solution 7.2%, USP
Iron	Colloidal ferric oxide; iron dextran	None	---	Phenol; sodium chloride*; hydrochloric acid/sodium hydroxide (for pH adjustment)*; water for injection*	Iron	Ferrextran 100; Felac; Imposil; Iron Dextran Injection; Iron Dextran 20% Injection; Iron Hydrogenated Dextran Injection; Nonemic; PVL Iron Dextran Injectable; Rubrafer; Rubrafer S-100 Uniferon® 100; Uniferon® 200
Vitamin A	Vitamin A propionate; retinyl palmitate	Vitamin D and E	Cholecalciferol; d-alpha-tocopherol	Benzyl alcohol; ethyl alcohol; PEG-30 castor oil; N-methyl-d-pyrrolidone; propylene glycol di (octanoate /decanoate); polysorbate 80	Vitamin A, D, and E	Vita-Jec® E-AD
Vitamin B_1	Thiamine hydrochloride	None	---	Benzyl alcohol; disodium edetate	Vitamin B_1	VetOne Thiamine HCl Injection
Vitamin B_{12}	Cyanocobalamin	None	---	Ammonium sulfate; benzyl chloride; citric acid; sodium citrate; sodium chloride	Vitamin B_{12}	VetOne Vitamin B_{12} Injection; Vita-Jec® Vitamin B_{12}
Vitamin B Complex	Thiamine hydrochloride	Vitamin B_2; Vitamin B_3; Vitamin B_5; Vitamin B_6; Vitamin B_{12}	Riboflavin 5'-phosphate; niacinamide; pyridoxine hydrochloride; d-Panthenol; cyanocobalamin	Benzyl alcohol; butylated hydroxyanisole (BHA); citric acid; propyl gallate; propylene glycol	Vitamin B Complex	High Potency Vitamin B Complex; Super B Complex; Vita-Jec® Vitamin B Fortified; Vitamin B Complex HP
Vitamin C	Sodium ascorbate	None	---	3-mercaptopropane-1,2-diol; Disodium dihydrogen ethylenediaminetetraacetate; Methyl 4-hydroxybenzoate; Propyl 4-hydroxybenzoate	Vitamin C	Vita-Jec® C Injectable Solution
Vitamin K	Phytonadione	None	---	Benzyl alcohol; butylated hydroxyanisole; citric acid; dextrose monohydrate; sodium phosphate; polyoxyethylated fatty acid derivative	Vitamin K	Vita-Jec® K-1
Selenium	Sodium selenite	Vitamin E	*d*-alpha tocopheryl acetate	Benzyl alcohol; polysorbate 80; sodium hydroxide and/or hydrochloric acid may be added to adjust pH	Selenium and Vitamin E	Bo-Se®; Mu-Se®; Velenium®
Zinc, copper, manganese, and selenium	Zinc oxide	Copper, manganese, and selenium	Copper carbonate, manganese carbonate, and sodium selenite	Benzyl alcohol, ethylenediaminetetraacetic acid (EDTA), sodium hydroxide	---	Multimin® 90

*Information of the inclusion of these technical additives is provided in a drug product summary compiled for a product marketed in the UK that is similar to the iron dextran injectable products available in the US (Pharmacosmos A/S, 2024).

We found no evidence that any injectable formulas identified above include technical additives allowed at § 205.603(f) that are not found in comparable oral electrolyte formulations (both with and without calcium).

However, we identified several technical additives included in injectable formulas of vitamins and iron supplements that are not found in comparable oral formulations. AAFCO names a variety of technical additives in its 2024 Official Publication (AAFCO, 2024). The minor ingredients that we found in injectable formulas, but not in oral formulas, also do not appear in this publication as allowed technical additives. Hereafter, we list the relevant vitamins or minerals where we have confirmed the presence of one or more minor ingredients exclusive to injectable formulas and briefly describe their action in the formulation.

Iron

Phenol is a common preservative found in injectable iron supplements (FDA, 2025). Phenol exhibits antimicrobial activity against a wide range of microorganisms (Rowe et al., 2009). Aqueous phenol solutions of 1% w/v concentration are bacteriostatic, while stronger solutions are bactericidal.

Vitamin A

N-methyl-d-pyrrolidone (NMP) is sometimes present in vitamin A injectable products. NMP is an increasingly common solvent and extraction medium used in the formulation of pharmaceuticals (EPA, 2017). Vitamin A injectable supplements may also contain polyethylene glycol. Manufacturers can use water-based polyethylene glycol solutions (*e.g.,* PEG-30) either as suspending agents or to adjust the consistency of other suspending technical ingredients (Rowe et al., 2009). Polyethylene glycols can also act as emulsion stabilizers when manufacturers use them in combination with other emulsifiers.

Vitamin C

Vitamin C injectable supplements may contain thiols. While vitamin C is itself an antioxidant, thiols (*e.g.,* 3-mercaptopropane-1,2-diol aka monothioglycerol) can also act as antioxidants in an injectable formulation (Gabrič et al., 2022).[2] Monothioglycerol functions as an antioxidant by a method of competitive reactivity (Sharma, 2019). This means it is a more readily oxidized material, or reducing agent, relative to the active ingredient.[3] Consequently, the presence of monothioglycerol protects the active ingredient from oxidative degradation during manufacturing and storage of the supplement.

Manufacturers sometimes formulate vitamin C injectable supplements with disodium dihydrogen ethylenediaminetetraacetate (disodium EDTA). Disodium EDTA functions as a chelating agent in a wide range of pharmaceutical preparations, typically at concentrations ranging from 0.005 to 0.1% w/v (Rowe et al., 2009).

Another minor ingredient that can be present in vitamin C injectable supplements is ethyl 4-hydroxybenzoate (methyl paraben). This works as an antimicrobial agent (21 CFR 184.1490).

Vitamin K

Due to its poor water solubility, injectable vitamin K requires formulation with an emulsifying agent such as polyoxyethylated fatty acid derivatives or polysorbate-80 (AAFCO, 2024; Britt & Brown, 2018).

Vitamin K injectable supplements may also contain butylated hydroxyanisole (BHA), which is a synthetic antioxidant and preservative (Program, 2021; Veshaal et al., 2025).

Specific Uses of the Substance:

A balanced total ration typically provides livestock with adequate amounts of essential vitamins and minerals. However, there are circumstances when injectable supplements are necessary to provide quick, short-term treatment for urgent health issues. The root cause of these urgent health issues typically stems from either unusual environmental conditions or a change in the physical demands of the animal (Adams, 1995).

Oral formulations of vitamins, minerals, and electrolyte supplements can address dietary deficiencies that may exist within many livestock diets. However, there are limitations to oral supplements, including (Shastak & Pelletier, 2024; Whittier, 1997):

- inadequate supplementation levels for the larger animal unit (*e.g.,* herd)
- variability of individual animal consumption
- biological availability of the supplement formulation

By contrast, injectable supplements provide a known dose to an individual animal (Arthington et al., 2014; Caramalac et al., 2021).

[2] Antioxidants are compounds that can prevent the oxidation of other molecules.
[3] A reducing agent is a substance that donates electrons to another substance, and in the process is oxidized.

The bioavailability of the supplement formulation is a critical consideration.[4] Many factors affect bioavailability, including (Byrne & Murphy, 2022):

- animal physiological state
- chemical form of the supplement
- overall diet digestibility
- presence or absence of dietary antagonist factors
- environment

One of the significant drawbacks of oral micronutrient intake in ruminant livestock (*e.g.,* cattle, goats, and sheep) is reduced absorption due to interactions with other nutrients within the rumen (Somagond et al., 2023).[5]

Injectable supplements described below are standard treatment options for various health conditions found in cattle, sheep, goats, and swine (Spears & Weiss, 2014; Zimmerman et al., 2026). Injectable supplements are generally impractical for large flocks of poultry due to their labor-intensive nature (Shastak & Pelletier, 2024); however, poultry farmers may choose to use them for high-value birds within breeding flocks, where precise dosing and targeted supplementation are critical.

Organic producers and their veterinary care teams use several standard formulations of injectable supplements to address specific common health concerns (see *Combinations of the Substance*). The particular applications of these injectable supplements are discussed in further detail below.

Calcium and magnesium

The initialism “CMPK” refers to a veterinary supplement containing calcium, magnesium, phosphorus, and potassium. Veterinarians can administer CMPK solutions intravenously to treat grass tetany and milk fever (Department of Animal Sciences Dairy Barn, 2022; Ward & Powell, 2017). An animal with a magnesium deficiency may also have a calcium deficiency because magnesium has a functional role in maintaining calcium blood levels (Van Saun, 2024).

Milk fever

Along with ketosis (see the technical reports *Glucose* and *Propylene Glycol*), dairy cows are at considerable risk of experiencing calcium deficiencies around the time of calving (Rana, 2024). Daily calcium excretion increases significantly during this period with the onset of milk production. This change can make it challenging for cows to maintain regular, necessary blood calcium concentrations. Many cows recover quickly from this imbalance. However, cows that suffer severe decreases in blood calcium concentrations and/or maintain low blood calcium concentrations (hypocalcemia) experience a health condition commonly called "milk fever," which may require medical attention (Cockcroft, 2015; Rana, 2024). Cows that are unable to stand require immediate correction of this condition by intravenous calcium infusion (Cockcroft, 2015). CMPK injectable supplements marketed for the treatment of milk fever may contain a combination of (Oetzel, 2017):

- dextrose (D-glucose)
- calcium
- magnesium
- phosphorus
- potassium

The additional electrolytes and glucose included in these formulations may not be necessary, or even beneficial, to a cow with milk fever (Braun & Jehle, 2007; Goff, 1999; Oetzel, 2017). Cows suffering from milk fever typically also have the following blood chemistry levels (Oetzel, 2017):

- low blood phosphorus
- high blood magnesium
- high blood glucose levels
- normal to slightly low blood potassium levels

The phosphorus source (hypophosphites) manufacturers typically use in CMPK injectable supplements is also not biologically available to the cow (Braun & Jehle, 2007; Goff, 1999; Oetzel, 2017). Manufacturers use phosphite salts in these products because they are very soluble in water and remain soluble even in the presence of calcium and magnesium (Goff, 1999). Phosphate is a biologically available phosphorus source. Manufacturers cannot use this form in formulations containing calcium or magnesium though without causing precipitates to form (Goff, 1999;

[4] Bioavailability refers to the proportion of an ingested material that is absorbed, transported to its site of action within the animal body, and converted to the form of the material the body uses.

[5] Ruminants are hoofed mammals, including cattle, sheep, and goats, with a unique digestive system. These animals have four stomachs, one of these stomachs is the rumen. The rumen also sometimes called the “paunch,” acts as a fermentation vat by hosting microbial fermentation that allows the animal to effectively derive energy from fibrous plant material.

Oetzel, 2017). However, for the majority of cows with milk fever and concurrent low blood phosphorus levels, the phosphorus levels do self-correct once the cow recovers from the hypocalcemia (Oetzel, 2017).

When veterinarians observe this combination of blood profiles in livestock, they can make informed decisions on the appropriate electrolyte combination for treatment. Calcium borogluconate (calcium gluconate with the addition of boric acid) alone is another common treatment for milk fever (Cockcroft, 2015; Rana, 2024). Calcium borogluconate is the standard choice because it typically causes less tissue irritation (Rana, 2024). The addition of boric acid increases the solubility of the calcium gluconate in the formulation (Rana, 2024).

Grass tetany

Low levels of magnesium in the blood cause a health condition commonly referred to as "grass tetany" (Van Saun, 2024). Veterinarians observed that cattle can develop grass tetany throughout the year in the southern US, particularly on cool-season pasture grasses during periods of high moisture (Oetzel, 2017). In early spring and fall, grasses often have high potassium concentrations due to cool, wet growing conditions (Van Saun, 2024). The rumen's efficiency in absorbing magnesium may decrease when potassium and nitrogen levels are high and sodium levels are low in the diet (Hindman, 2023). Low magnesium absorption leads to grass tetany. Grass tetany can be further compounded when farmers apply nitrogen and potash fertilizers to the pasture (Mullenix, 2018). Animals that graze on forage with low magnesium levels, as well as animals that may not be eating regularly, can present complicated cases of grass tetany (Van Saun, 2024).

Calving and milk production may also trigger grass tetany (Rana, 2024). Older, lactating cows are most prone to grass tetany (Cockcroft, 2015; Rayburn & Matlick, 2012). Cows most commonly experience this health issue in the first two months after calving. Calves fed on all-milk diet are also at risk, particularly at age 2 to 4 months (Cockcroft, 2015). Animals presenting with grass tetany are down or recumbent, and unable to rise. Cows with grass tetany need treatment with injections of both magnesium and calcium. Calcium is included because affected cows will also have low calcium levels in their blood. Additionally, intravenous calcium reduces the severity of potential side effects associated with magnesium injections (Oetzel, 2017).

<u>Electrolytes without calcium</u>

Animals constantly lose electrolytes through urine and gastrointestinal secretions (Barton & Kirby, 2016). The regulation and preservation of normal concentrations of these electrolytes support a variety of life-sustaining functions, including heart and brain function. Sick livestock frequently require fluid therapy to (Constable, 2003):

- correct tissue blood flow
- provide nutrients
- treat shock

Livestock that are unable to stand, show evidence of dehydration, or are unwilling to voluntarily ingest fluids orally require injectable fluid therapy (Constable, 2003). A veterinarian may recommend an injectable electrolyte supplement. Diarrheic calves often have low glucose levels and may benefit from the addition of dextrose (D-glucose) injections to their initial treatment of electrolytes (Constable et al., 2021). Oral electrolyte solutions can be used concurrently with and after injected fluid therapy to compensate for ongoing fluid and electrolyte losses (Doré et al., 2019).

<u>Iron</u>

Piglets are born with a minimal iron reserve (Neumann et al., 2010). Milk from the sow typically does not provide sufficient iron for piglets. Newborn piglets' ability to absorb iron is not fully developed (Starzyński et al., 2013). Consequently, oral iron supplementation is not the most efficient supplementation method. Piglets grow fast, and this can lead to the development of iron deficiencies, or anemia, unless a supplemental source of iron is available (Neumann et al., 2010). Pigs with access to outdoor spaces with soil generally do not require iron supplementation. The presence of intestinal parasites (*e.g.,* whipworms) is yet another condition that can lead to anemia in piglets (Rickard Ballweber, 2024). Piglets suffering from anemia that do not receive supplemental iron will rapidly begin to lose physical fitness, starting at one week of age (Neumann et al., 2010). Many livestock operations still consider iron supplementation a beneficial practice, even for piglets with access to soil.

Veterinarians can administer supplemental iron with an iron dextran injection (100-200mg) to counteract this deficiency (Neumann et al., 2010). Injectable supplementation is a standard practice and offers the advantage of providing precise dosing. Iron dextran should only be injected into the neck muscles to prevent any possibility of staining valuable areas of the carcass. For the same reason, iron dextran should not be administered by injection beyond seven days of age (Neumann et al., 2010).

<u>Selenium and vitamin E</u>

Scientists have documented selenium deficiencies in many species, including cattle, sheep, goats, and swine (Filley, 2014). White muscle disease is the most well-known health condition linked to selenium deficiency. The primary

symptom of the disease is the degeneration of muscle tissue. The skeletal and heart muscles of young livestock (3-8 weeks of age) are more sensitive to deficiency than those of older animals, although it can also be problematic for older animals. Selenium deficiency in cattle, sheep, and goats can lead to reproductive problems and reduced fertility, lowering live birth rates (Filley, 2014).

A selenium injection can prevent white muscle disease in young livestock because it quickly raises the selenium levels in the blood (Filley, 2014). Before birth, calves receive selenium through the placenta (Mehdi & Dufrasne, 2016). After birth, the cow's milk becomes the primary source of selenium for the calf. The biological availability of the selenium received through the placenta is greater than that from milk, and consequently, a selenium injection may be beneficial for calves (Mehdi & Dufrasne, 2016).

Veterinarians can administer injectable formulations containing selenium either subcutaneously (below the skin) or intramuscularly (into the muscle) (Filley, 2014). Subcutaneous delivery is ideal for meat quality purposes because it avoids contact with the food product (the muscle of the animal). Selenium and vitamin E are interdependent trace nutrients involved in similar biochemical pathways (Mehdi & Dufrasne, 2016). Therefore, a selenium deficiency could be partially compensated by an adequate intake of vitamin E and vice versa. A diet low in vitamin E may require more selenium to help prevent certain health conditions.

Livestock forage (*e.g.,* range, pasture, or hay) reflects the available selenium content of the soil where it grows (Filley, 2014). A low selenium content in the soil is not uncommon in the United States. Surveyors identified soil nutrient limitations in the Pacific Northwest, Northeast, Great Lakes, and Southeast regions. Frequent intake of an oral mineral premix can provide a concentrated source of selenium and other minerals when farmers add it to a complete ration. In one nationwide study, researchers observed that the percentage of severely selenium-deficient cattle was lower in all regions for operations that supplemented selenium, supporting the value of supplementation (Whittier, 1997). However, in some areas surveyed, supplementation procedures were frequently inadequate. Furthermore, producers in the Southeast region that used some supplementation still reported severe deficiencies in more than 16% of the sampled cattle (Whittier, 1997).

Vitamins A, D, and E

Deficiencies in vitamins A and E have overlapping health impacts for livestock (Shastak & Pelletier, 2024). These vitamins are essential for various biological functions, including growth and reproduction. Vitamin D has a role in maintaining the balance of calcium and phosphorus levels in livestock (Ahmadi Sheikhsarmast & Mohri, 2021). Vitamins A, D, and E can also inhibit oxidizing agents in the body and, consequently, enhance an animal's ability to resist oxidative stress (Ahmadi Sheikhsarmast & Mohri, 2021; Likittrakulwong et al., 2022). These functions are crucial in addressing several health challenges associated with calving and milk production in dairy cattle.

Shastak and Pelletier (2024) in a review of the literature observed that vitamin A may enhance sow reproductive performance. Vitamin E can also effectively improve reproductive performance in cows and sheep.

Vitamins B

The B vitamins are a chemically diverse group of vitamins that play essential roles as enzyme cofactors in central metabolic pathways in livestock (Girard & Graulet, 2021; Singh et al., 2024). There are eight B vitamins, including:

- thiamine (vitamin B_1)
- riboflavin (vitamin B_2)
- niacin (vitamin B_3)
- pantothenic acid (vitamin B_5)
- pyridoxine (vitamin B_6)
- biotin (vitamin B_7)
- folic acid (vitamin B_9)
- cobalamin (vitamin B_{12})

B vitamins are commonly available in a mixture, or "complex," but vitamin B_1 and vitamin B_{12} are also available individually (see *Combinations of the Substance*).

The necessity for supplementation of vitamin B-complex in ruminants remains a topic of debate among researchers (Girard & Duplessis, 2023). Microorganisms present in the rumen organ can produce these vitamins (Girard & Graulet, 2021). However, scientists have also observed improved metabolic efficiency and milk production linked to vitamin B supplementation. Research indicates that the demand for B vitamins frequently exceeds the supply from the diet and rumen microbes, particularly just before calving and during early lactation (Girard & Duplessis, 2023; Girard & Graulet, 2021). Veterinarians may administer injectable vitamin B_1 or a vitamin B complex as part of the treatment plan for dairy cattle during this period.

It is possible for ruminants to suffer from a vitamin B_1 deficiency (Gibbons, 2024; Soto-Blanco & Câmara, 2025). This deficiency may be caused by diets that include a high grain content and/or plants containing thiaminase enzymes (Soto-Blanco & Câmara, 2025). Symptoms include blindness, incoordination, and/or the inability to stand (Gibbons, 2024). The associated disease is polioencephalomacia (PEM) and researchers historically attributed it solely to an animal's altered thiamine status (Gibbons, 2024; Soto-Blanco & Câmara, 2025). However, current research continues to investigate an additional factor, high dietary sulfur intake. Veterinarians may administer injectable vitamin B_1 or vitamin B-complex to restore vitamin B_1 levels as part of the treatment for this disease (Currin, 2010; Soto-Blanco & Câmara, 2025).

Vitamin B_{12} aids in the conversion of propionate to glucose in livestock (Kang et al., 2025). This conversion helps prevent the accumulation of ketones and the development of ketosis-like conditions.[6] Ketosis is a common metabolic disease in dairy cows that often occurs 2–4 weeks after calving. Veterinarians may administer injectable vitamin B_{12} as part of the treatment for advanced ketosis.

Vitamin C

Vitamin C can inhibit oxidizing agents in the body and, consequently, enhance an animal's ability to resist oxidative stress (Likittrakulwong et al., 2022). Vitamin C also converts vitamin E to its active form. Cattle, sheep, goats, and swine can make vitamin C from glucose in the liver or kidneys (Akinmoladun, 2021). For this reason, vitamin C is not an essential dietary requirement for them. However, the concentration of vitamin C in the body of animals experiencing stress or disease can decrease. This may be related to low rates of vitamin C production, an increase in demand for the vitamin, or a combination of both (Akinmoladun, 2021).

The demand for glucose is elevated in lactating dairy cows because of the large amount of lactose made during milk production (Matsui, 2012). Glucose is the precursor material for vitamin C in livestock. It is unclear whether the stage of milk production consistently impacts vitamin C levels in dairy cows, but there is some evidence that it can be affected. Ketosis and mastitis (infection and inflammation of the udder) are other health conditions that may benefit from injectable vitamin C treatment (Matsui, 2012).

Vitamin K

Scientists currently understand that bacteria in the rumen of cattle, sheep, and goats produce sufficient quantities of vitamin K to meet their dietary requirements under most conditions (Bailey, 2017; Spears & Weiss, 2014). However, this is not the case when these animals are fed moldy legume hay or silage, particularly sweet clover (Bailey, 2017). Vitamin K aids prothrombin production in the liver. Dicumarol produced in moldy sweet clover hay interferes with this process. Low levels of prothrombin in the blood result in longer blood clotting time and subsequent internal bleeding. Similarly, certain components found in moldy feed can interfere with vitamin K synthesis in pigs (Ullrey, 1991). An injection of vitamin K and removal of the moldy feed or forage are the most effective ways to overcome low prothrombin levels and related internal bleeding (Alstad et al., 1985).

Zinc, copper, manganese, and selenium

Zinc, copper, manganese, and selenium are trace minerals commonly available in a combined formulation (see *Combinations of the Substance*) and they are essential for dairy cow health and milk production (Somagond et al., 2023). These trace minerals can inhibit oxidizing agents in the body and consequently enhance an animal's ability to resist oxidative stress. They are also immune system modulators. Dairy cows undergo major metabolic changes and a period of immunosuppression immediately before calving and throughout early lactation. These changes are commonly associated with a decrease in the blood concentrations of trace minerals (Somagond et al., 2023). To combat these deficiencies, veterinarians may administer injectable trace minerals as part of the treatment plan for dairy cattle during these periods.

Evaluation Questions

Classification of the Substance:

The NOSB previously received technical reports for electrolytes, vitamins, and minerals (NOP, 2015, 2019, 2024b). The authors provided in-depth detail related to the sourcing of the raw materials, the manufacturing processes, and a discussion on their nonsynthetic/synthetic status. We found no evidence to suggest that injectable supplements diverge from oral supplements in these aspects. Therefore, parts A, B, and C are omitted from *Evaluation Question #1* in this report.

We address parts D and E of *Evaluation Question #1* here because we understood that they are critical for the NOSB in its sunset review of these materials. Scientists continue to research manufacturing methods related to the

[6] Ketones are molecules the animal body makes when it is using fat instead of glucose for energy. Typically, livestock get most of their energy from glucose from dietary carbohydrates. When livestock cannot obtain enough energy from carbohydrates, their body breaks down fats for energy instead.

application of nanoparticles and excluded methods in the production of nutritional supplements. Consequently, we understood that there could be new information available and relevant to sunset review, as relates to these aspects of injectable supplements.

Below, we provide the most up-to-date information available regarding nanoparticles and excluded methods used to produce these materials.

Evaluation Question #1(D): Does this substance (in its raw or formulated forms) contain nanoparticles?
According to NOP Policy Memo 15-2 *Nanotechnology*, nanotechnology is conducted at the nanoscale, which is about 1 to 100 nanometers (nm) (NOP, 2024a). The NOP uses the term "incidental nanomaterials" to refer to substances that are byproducts of other manufacturing (*e.g.,* homogenization, milling) or that occur naturally (NOP, 2024a). The distinction between engineered and incidental may not always be clear.

Electrolytes and minerals
Nanomaterials can occur naturally in several minerals, and may also be incidental byproducts of human activity, such as homogenization or milling (Hochella et al., 2019).

Scientists have engineered nano-Se (selenium), and some evidence indicates that this form offers an advantage over conventional selenium supplementation, including enhanced mucosal permeability and higher intestinal absorption. Consequently, nano-Se has greater bioavailability and also exhibits reduced toxicity and lower antagonism with other minerals compared with other sources of selenium (Libera et al., 2021). Scientists have also engineered zinc and copper nanoparticles (Kazemi, 2025; Lee & Kim, 2025). Nano minerals have a larger surface area and higher absorption rates compared with larger mineral supplements. However, the safety of nanoparticles and their potential environmental impacts are areas of continuing research Current research on these materials is focused primarily on feed supplements rather than injectable supplements. We found no evidence that these engineered nanomaterials are commercially available in injectable supplements.

Vitamins
Advances in nanotechnology make it possible to produce nano encapsulate and nano emulsion vitamins (NOP, 2024b). Fat-soluble vitamins (A, D, E, and K) appear to be promising for use in nanoencapsulation (Kazemi, 2025). Some researchers indicated that vitamin D may be suitable for nanoencapsulation as an injectable supplement (Katouzian & Jafari, 2016). However, much of the nanoencapsulation and nano emulsion research is currently focused on oral supplements (Kazemi, 2025). We found no evidence that these engineered nanomaterials are commercially available.

Evaluation Question #1(E): Is this substance created using excluded methods?

Electrolytes and minerals
The active ingredients in injectable electrolyte and mineral supplements are inorganic substances. Consequently, manufacturers cannot use excluded methods to genetically manipulate these materials. However, one of the precursors used to produce sodium lactate by chemical synthesis is lactic acid. Lactic acid is a product of fermentation and, therefore, at high risk of being produced by genetically engineered microbes (NOP, 2015).

Sodium lactate
Manufacturers typically make sodium lactate by reacting sodium hydroxide with lactic acid (21 CFR 184.1768). Microbial fermentation accounts for over 90% of global lactic acid production (Ojo & de Smidt, 2023). Lactic acid-producing bacteria (LAB) (*e.g., Bacillus* sp., and *Corynebacterium glutamicum*) convert glucose to lactic acid. Filamentous fungi (*e.g., Rhizopus oryzae* and *Rhizopus arrhizus*) can also produce lactic acid. Molasses and whey are common materials that can provide the glucose component for lactic acid production. As of 2020, only nongenetically engineered LAB strains were granted FDA approval (Plavec & Berlec, 2020).

Molasses and whey are the most common low-cost food processing byproducts that manufacturers use as substrate for lactic acid production (Ojo & de Smidt, 2023). Sugar beets are the precursor material for sugar beet molasses, and these may be genetically engineered for pest related purposes (USDA, 2018c). Over 90% of beet farms in the USA and Canada grow bioengineered sugar beets (H7-1; glyphosate-tolerance). Consequently, in a 2018 crop summary, the USDA suggested that all sugar beets produced in these two countries should be presumed to be bioengineered sugar beets (USDA, 2018c).

Vitamins
All vitamins produced through fermentation are at risk of being produced with excluded methods (NOP, 2024b; Nupur et al., 2025). This was discussed in depth in the 2024 *Vitamins* (Livestock) technical report (NOP, 2024b). While some vitamin sources may not be produced from genetically engineered organisms, we could not categorically verify such claims for any vitamin due to the lack of publicly available information.

Manufacturers commonly produce vitamin B_3 (niacin), vitamin B_5 (pantothenic acid), and vitamin K (phytonadione) by chemical synthesis. Manufacturers may also produce these by a combination of chemical steps and microbial/enzymatic steps (Kang et al., 2022; Vandamme & Revuelta, 2016); however, we could not confirm the commercialization of these methods.

Only four vitamins have a high risk of being derived directly from excluded methods because they are produced with genetically engineered organisms (NOP, 2024b):

- vitamin B_2
- vitamin B_{12}
- vitamin C
- vitamin E

Vitamin B_2 (riboflavin)

Manufacturers commonly produce vitamin B_2 with engineered strains of *Ashbya gossypii* (fungi) and *Bacillus subtilis* (bacteria) (Averianova et al., 2020). In the past, scientists used classic techniques to induce mutagenesis in *A. gossypii* through chemical and radiation treatments; they have since adopted modern strategies of metabolic engineering (Revuelta et al., 2016). Manufacturers now use precise genetic engineering methods to construct production strains of both microorganisms with the trait of riboflavin overproduction (Averianova et al., 2020). These methods include gene amplification and replacement of wild-type regulatory regions of genes associated with riboflavin synthesis (Averianova et al., 2020; Revuelta et al., 2016).

Vitamin B_{12} (cobalamin)

Manufacturers have applied genetic engineering to improve the production of B_{12} by *P. denitrificans* and *P. freudenreichii* (Marie Sych et al., 2016). Similarly with vitamin B_2 production strains, in the past, scientists used classic techniques to induce mutagenesis through chemical and radiation treatments; they have since adopted modern strategies of metabolic engineering (Balabanova et al., 2021). Scientists have increased the production capacity for vitamin B_{12} by these microorganisms using a variety of methods including (Balabanova et al., 2021):[7]

- overexpression of genes for cobalamin production by insertion of genes from *Rhodobacter sphaeroides*
- removal of riboswitches for an entire gene cluster, paired with an exchange of promoters
- activation of silent genes in ribosomes

Vitamin C (ascorbic acid)

Vitamin C occurs naturally in various vegetable sources, including the juice of citrus fruits (Rowe et al., 2009). However, the preferred method of production involves a two-step fermentation process of synthetic chemicals (Tucaliuc et al., 2022). Manufacturers use the bacteria *Gluconobacter oxydans* in the first step of this process. The second step involves a combination of the bacteria species *Ketogulonigenium vulgare* and *Bacillus megaterium*. Manufacturers may also produce it using a common synthetic procedure that employs *Acetobacter suboxydans* or *Acetobacter xylium* in just one step of the process (Tucaliuc et al., 2022). In 2011, scientists introduced folate biosynthesis pathway genes from *Lactococcus lactis* to wild-type *K. vulgare* to improve the growth and 2-keto-l-gulonic acid (vitamin C precursor) production rates of the *K. vulgare* (Cai et al., 2011). Researchers in this field now aim to develop a new engineered strain which combines the metabolic traits of *K. vulgare* and the companion strain (*Bacillus spp.)* and is able to produce more vitamin C from the chemical precursors in a single step fermentation process (Yang & Xu, 2016).

Vitamin E (tocopherol)

Manufacturers produce injectable vitamin E by extraction or molecular distillation of steam distillates of vegetable (corn and soybean) oils (Rowe et al., 2009). Corn and soybeans produced in the U.S. are often genetically modified (USDA, 2018a, 2018b).

Technical additives

Some technical additives present in injectable supplement formulations are at high risk of production from genetically engineered source material, including (NOP, 2014, 2022, 2023):

- dextrose (D-glucose)
- ethanol
- citric acid
- sodium citrate

[7] Riboswitches and promoters are regulatory molecular elements involved in the cellular process of producing proteins, also known as translation. Ribosomes are the cellular location where translation occurs.

Dextrose (D-glucose)
Dextrose occurs naturally in plants. Manufacturers typically use acid or enzymatic hydrolysis of starch to produce dextrose (Rowe et al., 2009). Corn is a common source of starch used in the production of dextrose. Corn produced in the U.S. is often genetically modified (USDA, 2018a).

Ethanol
To produce ethanol (ethyl alcohol), manufacturers utilize enzymatic fermentation of starch, sugar, or other carbohydrates (Rowe et al., 2009). Corn is a common starch source used for the production of ethanol (Walker & Walker, 2018). As previously mentioned, corn produced in the U.S. is often genetically modified (USDA, 2018a).

Citric acid and sodium citrate
Manufacturers produce approximately 90% of the world's citric acid by microbial fermentation of *Aspergillus niger* (Khurshid et al., 2024). Based on available information, the majority of citric acid manufacturers use wild type fungal strains, as well as those that are products of classical induced mutagenesis (NOP, 2023).[8] The development of genetically engineered microorganisms for citric acid production is an area of continuing research (Yuan et al., 2024). We found no evidence to suggest these genetically engineered organisms are commercially available. More information on the details of these excluded methods can be found in the 2023 *Citric Acid* technical report, beginning on line 112 (NOP, 2023). Information related to the microbial origin of commercially available citric acid products is often not publicly available.

Chemical synthesis is likely used in the production of citrate materials (*e.g.,* sodium citrate); however, manufacturers typically make sodium citrate by adding sodium carbonate to a solution of citric acid until effervescence ceases (Rowe et al., 2009). The citric acid precursor material is a product of fermentation and, therefore, is at high risk of being produced by genetically engineered microbes (NOP, 2015).

Corn steep liquor is the primary substrate used in the industrial production of citric acid (Xue et al., 2021). Manufacturers may also use molasses from sugarcane or sugar beet varieties (Behera et al., 2021; Hu et al., 2019). Corn is the precursor material for corn steep liquor, and corn produced in the U.S. is often genetically modified (USDA, 2018a). Sugar beets are the precursor material for sugar beet molasses, and these are often genetically engineered (USDA, 2018c).

Environment and Human Health Effects
Most drug products approved by the Center for Veterinary Medicine (CVM) at the FDA undergo at a minimum, a Phase 1 environmental impact assessment (FDA, 2024a; The International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH), 2000). In Phase I, the manufacturer investigates the potential for environmental exposure impact based on the intended use of the product. This is equivalent to either a categorical exclusion or an environmental assessment conducted under the National Environmental Policy Act (FDA Center for Veterinary Medicine, 2019a). Phase I also identifies products that require a more extensive assessment under Phase II. Any product approved for use in confinement (*e.g.,* swine barns, poultry facilities, etc.) typically also has to undergo a Phase 2 environmental impact assessment (The International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH), 2004). In Phase II, the manufacturer prepares more extensive data than Phase I, this includes environmental fate and toxicity studies (FDA, 2019). The environmental assessment (EA) documentation is submitted with the application materials for consideration by the CVM (FDA, 2024a). If the FDA determines that the drug will not significantly impact the environment based on the information in the EA, the agency writes a "Finding of No Significant Impact" (FONSI). If the FDA determines that the drug will significantly impact the environment, the agency writes an "Environmental Impact Statement" (EIS) (FDA, 2024a).

The CVM also compiles a Freedom of Information (FOI) Summary that provides the public with a summary of the key information the FDA considered prior to the approval or conditional approval of an animal drug product (FDA Center for Veterinary Medicine, 2025b). The FOI Summary will include information related to aspects of both animal safety and human safety.

Below we summarize the information that is publicly available on the 15 animal drug products currently approved by the FDA that are also allowed as nutritive supplements at § 205.603(a)(21) (see *Table 3*). These 15 animal drug products appear in the Green Book at the time of this report (FDA Center for Veterinary Medicine, 2025a). New animal drug products that the FDA determines are safe and effective may receive an approval, conditional approval, or indexed listing (see FDA Oversight). Most approved and conditionally approved animal drugs appear in the Green Book.

[8] In classical mutagenesis scientists and producers initiate the process by exposure to UV light, chemicals, irradiation, or other stress-causing activities. The NOP noted in NOP Policy Memo 13-1 *Cell Fusion Techniques used in Seed Production* that classical mutagenesis is a method scientists and producers use in traditional breeding programs (NOP, 2013b).

Indexed listings do not appear in the Green Book. However, there are no animal drugs with indexed listings that are marketed for use in early, non-food life stages of a food-producing minor species currently (FDA Center for Veterinary Medicine, 2025c). Extra-label use of approved human and animal drugs by a veterinarian is permitted under AMDUCA (21 CFR 530). We were unable to find information identifying additional drug products that a veterinarian might administer to provide vitamins, minerals, or electrolytes in an injectable form under AMDUCA.

The EA and FOI documents were not readily available for each of the 15 animal drug products that currently appear in the Green Book for use in food-producing animals, as indicated by the not available (NA) designation in the table. These documents are subject to the Freedom of Information Act (FOIA) and ostensibly available upon request from the FDA. We submitted a formal request for these documents; however, no additional information was provided to us.

Table 3: FDA approved injectable food animal drug substances with active ingredients that are vitamins, minerals, or electrolytes (FDA Center for Veterinary Medicine, 1985, 1998a, 1998b, 2024c, 2025a)

Proprietary Name	NADA or ANADA No.	Active Ingredients	Species	Animal Safety	Human Food Safety	Environmental Assessment
MULTIMIN® 90	141-582	Zinc, copper, manganese, and selenium	Cattle-not for use in pregnant cows during their first trimester; not for use in beef calves less than 2 mos., dairy calves, and veal calves	Selenium and copper toxicities if overdosed; safe when used according to the labeling	FDA estimated low risk for development of bacterial antimicrobial resistance and exposure to residues of the four minerals via diet; 14-days withdrawal period and a milk discard time of 0-days.; FDA determined reasonable certainty of no harm for residues of the four minerals; Due to high mineral concentrations there is a potential risk of zinc, copper, manganese, and selenium toxicity in people who handle or are exposed to the drug.	The product is not expected to pose an unacceptable risk for the environment when used according to the labeling.*
Ferrextran 100	010-865	Iron dextran complex	Swine, piglet	NA	NA	NA
Felac	011-644	Colloidal ferric Oxide	Swine, piglet	NA	NA	NA
Nonemic	010-793	Iron dextran complex	Swine, piglets	NA	NA	NA
Rubafer Rubafer S-100	011-879	Iron dextran complex	Swine, piglets	NA	NA	NA
Imposil	099-667	Iron dextran complex	Swine, piglets	NA	NA	NA
Uniferon® 100	106-772	Iron dextran complex	Swine, piglets	NA	NA	NA
Uniferon® 200	134-708	Iron dextran complex	Swine, piglets	NA	NA	NA
PVL Iron Dextran Injectable	119-142	Iron dextran complex	Swine, piglet	NA	NA	NA
Iron Hydrogenated Dextran Injection IRON DEXTRAN 20% INJECTION	138-255	Iron dextran complex	Swine, piglets	Product is safe for prevention and treatment of iron-deficiency anemia in pigs.	No human safety concern for residues when used according to labeling; A withdrawal period is not required	NA
Iron Dextran Injection Iron Dextran Injection 100mg	200-254	Iron dextran complex	Swine, piglets	Product is safe when used according to the labeling.	A tolerance has not been established for iron dextran; A withdrawal period for iron dextran injection has not been established	NA
Iron Dextran Injection - 200	200-256	Iron dextran complex	Swine, piglets	Product is safe when used according to the labeling.	A tolerance has not been established for iron dextran; A withdrawal period for iron dextran injection has not been established	NA
Bo-Se	012-635	Vitamin E and selenium	Sheep, restricted during pregnancy; swine, weanlings and sows; cattle, calves and beef	NA	NA	NA
Mu-Se®	030-314	Vitamin E and selenium	Cattle, calves and beef cows	NA	NA	NA
Velenium™	200-109	Vitamin E and selenium	Cattle, calves and beef cows	Product is safe when used according to the labeling.	Discontinue use 30-days before the treated cattle are slaughtered for human consumption.	NA

*This is information provided by a report from The Health Products Regulatory Authority (HPRA) compiled for review of a product available in Europe that is similar to the Multimin® 90 product available in the US (Health Products Regulatory Authority, 2020).

Evaluation Question #6: Discuss the effects of this substance on biological and chemical interactions in the agroecosystem. Include the physiological effects of this substance on soil, crops, livestock, or other organisms (such as aquatic) that could be affected by this substance when used as petitioned [7 U.S.C. 6518(m)(5)].

The fluctuations in vitamins, minerals, and electrolytes through livestock are tightly regulated (Daniel et al., 2023). The complex mechanisms of metabolism regulate the rate of absorption from the gut as well as the amount of excretion through feces and urine (see Impacts on crops, soil, and ecosystem biodiversity). In the case of lactating animals these materials are also excreted through the milk. An excess of these nutrients can occur either from high dietary intake or from the body releasing them from its own tissue stores (Daniel et al., 2023).

Scientists at Kansas State Veterinary Diagnostic Lab observed cattle with medical histories indicating mineral over-supplementation (Henningson, 2016). They concluded that multiple sources of mineral supplement and/or a large injectable dose can result in overdoses leading to acute organ damage (see *Impacts on livestock*).

Impacts on crops, soil, and ecosystem biodiversity

The risk of accumulation of vitamins and minerals within the environment is an area of current research. However, in the studies we found, scientists focused on nutrients excreted due to over supplementation with feed additives rather than injectable supplements (Brugger & Windisch, 2015; Shurson et al., 2022). Most drug products approved by the FDA provide details related to the environmental impact of the material (FDA, 2024a). However, the EA documents were not readily available for any of the FDA approved products.

We found no supplementary information related to direct or indirect effects of injectable supplements as used in livestock production on plant life, soil, or ecosystem biodiversity.

Impacts on livestock

The FOI Summary provides information directly related to animal safety of FDA approved animal drug products. The FOI Summaries were not readily available for most of the FDA approved products. The ones that were available generally indicated that specific injectable products were safe for animals when used as labeled (FDA Center for Veterinary Medicine, 1985, 1995, 1998b, 1998b, 2024c):

- Iron Hydrogenated Dextran Injection IRON DEXTRAN 20% INJECTION (iron dextran complex)
- Iron Dextran Injection Iron Dextran Injection 100mg (iron dextran complex)
- Iron Dextran Injection Iron Dextran Injection 200mg (iron dextran complex)
- Velenium™ (vitamin E and selenium)

The FDA in the FOI Summary for MULTIMIN® 90 notes that both copper and selenium are known to be toxic if overdosed and consequently if the drug product is used with other sources of these minerals, cattle may show clinical signs associated with those toxicities, including death (FDA Center for Veterinary Medicine, 2024a). The details of copper and selenium toxicities are discussed later in this report (see Zinc, copper, manganese, and selenium below). The FDA did not express the same selenium toxicity concern within the FOI Summary for Velenium™ (vitamin E and selenium) (FDA Center for Veterinary Medicine, 1995).

Injectable supplements are standard treatment options for a variety of health conditions in cattle, sheep, goats, and swine (see *Specific Uses of the Substance*). However, the method of delivery of injectable supplements itself may cause inflammation and lesions at the injection site of food animals (Arthington & Ranches, 2021; FDA Center for Veterinary Medicine, 2024a; Van Donkersgoed et al., 2000).

Additional information related to injectable supplement ingredients is limited. Factors influencing any toxic responses to veterinary therapeutic agents are numerous and their interactions complex. These factors include (Anadón, 2016):

- chemical character of the toxicant
- route of exposure
- duration of exposure
- intensity of exposure
- domestic species
- sex of the animal
- age of the animal
- preexisting disease state
- nutritional status
- prior exposure to the toxicant, or related compounds

B vitamins, vitamin C, and vitamin K are generally nontoxic (Adams, 1995). However, there are select vitamins and minerals that, when injected, may pose additional health risks.

Calcium and magnesium

Animals have a wide range of tolerance for calcium levels (Adams, 1995). However, any rapid injection of calcium exposes the cow to additional risk for (Oetzel, 2017):

- heart failure
- imbalance of calcium homeostasis
- relapse of low calcium blood levels

The rapid injection of calcium can induce heart complications starting at blood concentrations of about 7.0 to 8.0 mmol/L (28 to 32 mg/dL) (Oetzel, 2017). Normal blood calcium levels in cows range between 8.5 and 10 mg/dL (Potts, 2022). The administration of a single dose of intravenous calcium increases average blood calcium levels to about 4.8 mmol/L (19 mg/dL) (Oetzel, 2017). Scientists have not reported the exact rate of risk for cardiac arrest following intravenous calcium administration. A very low percentage of cows are affected, but the potential risks of giving intravenous calcium are sufficient to preclude its use in cows that have not yet developed late stages of milk fever with dangerously low calcium concentrations in their blood (Oetzel, 2017).

A more common problem with intravenous calcium administration is that it quickly and directly impairs parathyroid hormone release in cattle (Oetzel, 2017). An increase in parathyroid hormone release is the typical metabolic response to low calcium concentrations in the blood. This biochemical mechanism is necessary for the cow to survive the period of negative calcium balance that occurs during early lactation.

Low calcium blood levels also stimulate the release of calcitonin hormone (Oetzel, 2017). The uptick in calcitonin hormone levels in cattle inhibits calcium resorption in the kidneys and increases bone deterioration. The combined result of lower parathyroid hormone release and increased calcitonin release following intravenous calcium administration can inhibit the cow's natural ability to maintain calcium homeostasis (Oetzel, 2017). This may lead to a relapse of milk fever.

Manufacturers commonly combine calcium with magnesium in injectable supplements that veterinarians may use to treat grass tetany. This is in part because intravenous calcium reduces the severity of the potential side effects of magnesium administered by injection, which may include weakening of the lungs and heart attack (Oetzel, 2017). Fatal convulsions may also occur in animals that are stimulated during treatment (Oetzel, 2017).

Other components of some multiple electrolyte solutions containing both calcium and magnesium may be unnecessary (*e.g.,* phosphorus and potassium) (Oetzel, 2017). Some technical additives may also be potentially harmful. This includes glucose, since cows with clinical grass tetany are also likely to have elevated blood sugar levels.

Iron

Iron dextran preparations are generally non-toxic (Svoboda et al., 2017). Reports of toxicity related to iron dextran injection are irregular. Acute toxicity can occur when piglets are deficient in antioxidants (*e.g.,* vitamin E and selenium). These animals have reduced resistance to iron toxicity because excess free iron can enable the increased production of free radicals. Symptoms of iron toxicity may include (Svoboda et al., 2017):

- shortness of breath
- tremor
- movement incoordination
- paralysis
- coma
- heart failure

Scientists observed the increased accumulation of free radicals can result in cellular damage of the liver and small intestine, even at UL iron doses (Ding et al., 2020, 2021). Piglets may also experience reduced weight gain when given UL iron doses (Ding et al., 2021).

Selenium and vitamin E

Selenium injection overdose can be lethal (Filley, 2014). Acute selenium toxicity usually occurs within a few hours to two days after oral overconsumption or injection. Clinical signs can include pulmonary, cardiac, liver, and kidney damage (Henningson, 2016).

Vitamins A, D, and E

Vitamin A and D are both toxic at high doses (Adams, 1995). Vitamin A toxicity can interfere with an animal's ability to metabolize vitamins D, E, and K. Upper safe limits of vitamin A are between 4-10 times the nutritional requirements for non-ruminants and as much as 30 times the nutritional requirements for ruminants (Adams, 1995).

Vitamin D toxicity directly impacts the metabolism of calcium and phosphorus because it is a precursor material for a hormone that contributes to the regulation of calcium in the body (Adams, 1995). Consequently, animals suffering from this condition can experience excessive mobilization of calcium stores and hypertension. Vitamin D toxicity can also indirectly interfere with the metabolism of vitamins A, E, and K. The effects of these disturbances include changes in the ability of the blood to coagulate and cellular level antioxidant functions (Adams, 1995).

Vitamin E is relatively nontoxic compared to vitamins A and D (Adams, 1995). Researchers estimate upper safe limits for vitamin E are approximately 100 times the nutritional requirements for a variety of species. Excessive doses of vitamin E lead to changes in blood coagulation ability and exacerbation of vitamin K deficiencies in animals (Adams, 1995).

Zinc, copper, manganese, and selenium

Zinc toxicity can cause digestive tract inflammation, kidney damage, and liver damage (Henningson, 2016). The levels of bioavailable iron, copper, and manganese in livestock may also decrease as a result of elevated levels of zinc in the blood (Adams, 1995).

Acute copper toxicity often causes severe digestive tract inflammation and congestion of the liver, kidneys and spleen (Henningson, 2016). Chronic copper toxicity can result in an enlarged spleen, kidney damage, and liver damage. Researchers in the FOI Summary for MULTIMIN® 90 observed that cattle in the treatment group that received five-times the labeled dose suffered liver damage and associated blood chemistry changes caused by copper toxicity (FDA Center for Veterinary Medicine, 2024a).

Evaluation Question #8: Describe and summarize any reported effects upon human health from use of this 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)].

The FOI Summary provides human safety information directly related to the FDA animal drug under review. These summaries may include withdrawal periods for milk and meat producing livestock. Additionally, risks to human safety for anyone handling the drug product. The FOI Summaries were not readily available for most of the FDA approved products. The ones that were available generally indicated that specific injectable products were safe for use in food animals when used as labelled (FDA Center for Veterinary Medicine, 1985, 1995, 1998a, 1998b):

- Iron Hydrogenated Dextran Injection IRON DEXTRAN 20% INJECTION (iron dextran complex)
- Iron Dextran Injection Iron Dextran Injection 100mg (iron dextran complex)
- Iron Dextran Injection Iron Dextran Injection 200mg (iron dextran complex)

None of these products have a required withdrawal time (FDA Center for Veterinary Medicine, 1985, 1995, 1998a, 1998b). However, all these products are labeled for use only in piglets and do not indicate any use in animals near slaughter age.

The FOI Summary for MULTIMIN® 90 indicates a withdrawal period of 14-days and a milk discard time of 0-days (FDA Center for Veterinary Medicine, 2024a). In the summary, the FDA also estimated a low risk to human health related to the development of antibiotic resistant bacteria important in human medicine as a direct result of exposure to the trace metals in this product (FDA Center for Veterinary Medicine, 2024a). The FDA indicated exposure to residues of the four minerals through consuming meat and milk is low after comparing data from residue depletion experiments and either the ULs or recommended average daily intakes (ADIs) for each of the respective minerals. Due to the high mineral concentrations in MULTIMIN® 90, there is a potential risk of zinc, copper, manganese, and selenium toxicity in people who handle or are exposed to the drug product. Symptoms of these toxicities in people include aches, chills, nausea, vomiting, diarrhea, irregular heartbeat, abdominal pain, tremors, and irritability (FDA Center for Veterinary Medicine, 2024a).

The FOI Summary for Velenium™ prescribed discontinued use 30-days before the treated cattle are slaughtered for human consumption (FDA Center for Veterinary Medicine, 1995).

We found no additional information on the direct or indirect effects on human health from the use of injectable supplements in food animal healthcare. However, there are general human health concerns associated with extraneous supplementation and the accumulation of these substances in the milk and meat of food animals. These are described in further detail below.

Iron

Meat is one of the primary dietary sources of iron for humans. The biological availability of iron in meat, particularly in the heme form, is very high (Czerwonka & Tokarz, 2017). However, the tolerable upper limit (UL) for iron in humans and its implications on health are unclear at this time (Czerwonka & Tokarz, 2017; EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) et al., 2024). The Institute of Medicine (renamed the National Academy of Medicine) defines UL as the highest daily intake level of a nutrient that is likely to pose no risk of adverse health effects for almost all individuals (Institute of Medicine, 2000).

Vitamins A, D, and E

Liver, fish, eggs, and dairy products offer the highest dietary concentrations of vitamin A (retinol) (Office of Dietary Supplements, 2025). Most people do not regularly consume liver or liver products (Schulz et al., 2025). By contrast, milk consumption is considerably high in many countries. In Germany, people regularly exceed the recommended dietary levels of vitamin A. The European Food Safety Authority (EFSA) derived a tolerable UL for the daily intake of preformed vitamin A (*i.e.,* retinol and retinyl esters) of 3000 µg RE (retinol equivalent) for adults, including pregnant individuals, and of 800–2600 µg RE for younger age groups (Schulz et al., 2025). Scientists conducted a statistical analysis of preformed vitamin A levels found in liver and milk. They concluded that the estimated overall median dietary intake of preformed vitamin A for individuals aged 0.5 to 5 years did not exceed the age-specific upper intake levels. For population groups that consume animal liver, the scientists concluded that it could lead to high vitamin A intake and risk of exceeding the ULs (Schulz et al., 2025). A variety of health issues are associated with excess dietary vitamin A, ranging from minor to significant. These include (Chen et al., 2023):

- abdominal pain
- muscle aches
- impaired coordination of motion
- reduced bone density
- liver tissue alterations
- fetal development abnormalities in pregnant individuals

Zinc, copper, manganese, and selenium

The Health Products Regulatory Authority (HPRA), in a report compiled for review of a product available in Europe similar to the Multimin® 90 product available in the US, noted that prior to the review a large body of toxicity data on each of the mineral compounds (manganese carbonate, copper carbonate, zinc oxide and selenium selenite) included in the formulation already existed (Health Products Regulatory Authority, 2020). Furthermore, there is no maximum residue limit (MRL) for any of these minerals in the European Union. The MRL is the maximum allowed concentration of a residue in a food product obtained from an animal that has received a veterinary drug. Similar to the FDA during their review of the US product, the HPRA compared total residue amounts in meat from treated animals to published mineral ULs for adults to determine an appropriate withdrawal period (Health Products Regulatory Authority, 2020). Using this approach, an eight-day meat withdrawal period was proposed for the European product. A zero-day withdrawal period was proposed for milk in animals treated with the European product based on the lack of MRLs for these minerals. There was no further risk to humans based on the assessment when the supplement is used in cattle as directed in the product literature (Health Products Regulatory Authority, 2020).

Meat, eggs, and dairy are all sources of dietary zinc for humans (NIH, 2022a). At a sustained daily intake above 50 mg, zinc can interfere with copper absorption, reduce immune function, and lower HDL cholesterol levels in humans. The NIH reported dietary zinc is rarely as high as 50 mg and subsequently concluded dietary zinc is unlikely to cause zinc toxicity.

Organ meats (*e.g.,* liver and kidney) provide a concentrated source of dietary copper for humans (NIH, 2022b). Chronic exposure to high levels of copper can result in liver damage and digestive tract distress. The UL for copper for adults is 10,000 µg/day (NIH, 2022b). However, copper toxicity is rare in healthy individuals. Copper absorption from the intestine and copper release by the liver into bile are metabolically balanced in humans to provide protection from copper deficiency and toxicity (NIH, 2022b). It is unlikely that consuming animal products at typical dietary amounts would cause copper toxicity (Hassan & Albayati, 2025; NIH, 2022b).

Meat, eggs, and dairy are all sources of dietary selenium for humans (NIH, 2025). The UL for selenium for adults is 400 µg/day. Selenium toxicity can cause a range of significant symptoms including digestive tract distress, hair loss, tremors, and organ failure. However, researchers calculated from a nationwide survey that the average daily selenium intake in people age 2 years and older in the United States, from foods and beverages, is 108 µg/day (NIH, 2025). It is unlikely that consuming animal products at typical dietary amounts would cause selenium toxicity (Hassan & Albayati, 2025; Lei et al., 2022).

Meat, milk, and eggs do not provide dietary manganese for humans (NIH, 2021).

Necessity and Alternatives:

Evaluation Question #9: Describe all natural (nonsynthetic) substances or products which may be used in place of this substance [7 U.S.C. 6517(c)(1)(A)(ii)]. Provide a list of allowed substances that may be used in place of this substance [7 U.S.C. 6518(m)(6)].

We found no evidence of nonsynthetic or allowed substances that could be used in place of these injectable formulations. We reviewed primary literature and also consulted with veterinary professionals who affirmed that this

conclusion aligns with current best veterinary practices (R. Hunter, personal communication, October 20, 2025; M. Kleinhenz, personal communication, October 14, 2025).

Evaluation Question #10: Describe any alternative practices that would make the use of this substance unnecessary [7 U.S.C. 6518(m)(6)].

We found no evidence of specific alternative practices that would make the use of these injectable formulations unnecessary. We also consulted with veterinary professionals to affirm that this conclusion aligns with current best veterinary practices (R. Hunter, personal communication, October 20, 2025; M. Kleinhenz, personal communication, October 14, 2025).

Focus Questions

Focus Question #1: Are there any unique attributes to the injectable formulas of these substances relevant to National List criteria that NOSB should consider in its sunset review?

Yes. Injectable supplement formulas possess unique attributes relevant to the National List criteria. We provide information related to many of these attributes in the following sections and evaluation questions.

Table 4: Focus Question #1 conclusions

Section or evaluation question	Brief conclusion
Specific Uses of the Substance	A balanced total mixed ration (TMR) can typically provide livestock with adequate amounts of essential vitamins and minerals. However, there are circumstances when injectable supplements are necessary to provide quick, short-term treatment for urgent health issues.
Evaluation Question #1(D)	We found no evidence that manufacturers of commercial products currently use nanotechnology.
Evaluation Question #1(E)	There is some risk of manufacturers using excluded methods to manufacture certain ingredients in injectable supplement formulations.
Evaluation Question #6	Most drug products approved by the CVM at the FDA undergo at a minimum, a Phase 1 environmental impact assessment. Any product approved for use in confinement (*e.g.,* swine barns, poultry facilities, etc.) typically also has to undergo a Phase 2 environmental impact assessment. The related EA documentation is not publicly available currently, except by a FOIA request. The FOI Summary provides information directly related to animal safety of FDA approved animal drug products. The FOI Summaries were not readily available for most of the FDA approved products. However, the FDA notes in the FOI summary for MULTIMIN® 90 that both copper and selenium are known to be toxic if overdosed and consequently if the drug product is used with other sources of these minerals, cattle may show clinical signs associated with those toxicities, including death. There are also some general animal health concerns associated with the injection method and extraneous nutrient supplementation.
Evaluation Question #8	We summarize the information publicly available on the 15 animal drug products currently approved by the FDA that are also allowed as nutritive supplements at § 205.603(a)(21) (see *Table 3*). The relevant documents were not readily available for every product. There are some general human health concerns associated with extraneous supplementation and the accumulation of these substances in the milk and meat of livestock.
Evaluation Question #9	We found no evidence of nonsynthetic or allowed substances that could be used as alternative health treatments.
Evaluation Question #10	We found no evidence of alternative practices that would make the use of these substances unnecessary.

Additional details are available within these sections and evaluation questions.

Focus Question #2: Do any injectable formulas include excipients allowed via 205.603(f) that are not found in the non-injectable versions of electrolytes, vitamins, and minerals? If yes, please describe.

Yes, but very few. We cannot unconditionally verify this list is exhaustive due to the lack of publicly available information. However, we identified several technical additives included in injectable formulas of vitamins and iron supplements that are not found in comparable oral formulations below:

- phenol (iron injectable supplements)
- N-methyl-d-pyrrolidone (vitamin A injectable supplements)
- polyethylene glycol (vitamin A injectable supplements)
- 3-mercaptopropane-1,2-diol aka monothioglycerol (vitamin C injectable supplements)
- disodium dihydrogen ethylenediaminetetraacetate (vitamin C injectable supplements)
- ethyl 4-hydroxybenzoate (vitamin C injectable supplements)
- polyoxyethylated fatty acid derivatives (vitamin K injectable supplements)
- butylated hydroxyanisole (vitamin K injectable supplements)

For additional information, please see *Combinations of the Substance* and *Table 2*.

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