

## EPINEPHRINE

### Livestock

### Executive Summary

Epinephrine is a naturally derived hormone that is secreted from the adrenal glands as part of the sympathetic nervous system in mammals. In situations of high stress, epinephrine, commonly referred to as adrenaline, is secreted in order to help the individual cope with the stress; physiologically, it allows the individual to increase its heart rate, which in turn, increases the rate of glycogenolysis, creating more energy and allowing the individual to run faster, jump higher, and perform better.

As a medical drug, epinephrine is used to stimulate heartbeat and to treat emphysema, bronchitis, bronchial asthma and other allergic conditions, as well as in the treatment of the eye disease, glaucoma. Organic farmers are petitioning the use of epinephrine on animals in order to treat severe anaphylactic shock that occurs to livestock in reaction to certain injections of other legal antibiotics and vitamins. Without epinephrine treatment, especially in severe cases, the animal's life is in danger and if shock persists, it can cause death.

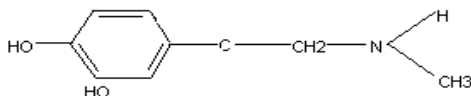
According to the OFPA ruling released by the USDA, hormones and enzymes are not allowed in organic animals. This, then, forbids the use of epinephrine. The following report gives an in depth analysis of epinephrine—its composition, its affects within the body, as well as its effect on the environment.

### Summary of TAP Reviewers' Analyses<sup>1</sup>

<i>Synthetic/ Nonsynthetic</i>	<i>Allow without restrictions?</i>	<i>Allow only with restrictions? (See Reviewers' comments for restrictions)</i>
Nonsynthetic (3)	Yes (0) No (3)	Yes (1) No (2)

### Identification

**Chemical names:** Epinephrine, C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>



**Other Names:** adnephrine, adrenal, adrenalin, 1-adrenlin, adrenaline, (-)-adrenaline, 1-adrenaline, adrenamine, adrenan, adrenapax, adrenasol, adrenine, adrenodis, adrenohorma, adrenosan, adrenutol, adrin,

<sup>1</sup> This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.

balmedren, 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-benzenediol, hemostasin, haemostasin, hektalin, hemisine, kidoline, levorenin, renalina, renoform, renostypticin, vasotonin, suprel, surrenine, tonogen<sup>2</sup>

**CAS Number:** 51-43-4

**Other Codes:** EINECS 200-098-7

## **Characterization**

**Composition:** Epinephrine is a naturally occurring amino acid based hormone belonging to the catecholamine class of neurotransmitters which is made up of an aromatic portion (catechol) attached to an amine (nitrogen-containing group).<sup>3</sup>

### **Properties:**

**Appearance:** off-white powder

**Melting Point:** 215 C where it decomposes<sup>4</sup>

**Molecular Weight:** 183.2066

**Volume:** 211.53 cubic angstroms

**Stability:** stable

**Compatibility:** incompatible with acids, acid chlorides, acid anhydrides, and oxidizing agents.

**Energy Measurement:** one molecule measured at -623.914 atomic units

**Dipole Moment:** 4.224 debye

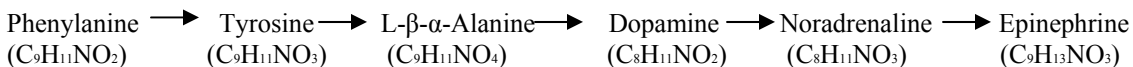
**Sensitivity:** light sensitive.

**Miscellaneous:** the molecule has 72 different vibrations<sup>5</sup>

### **How Made:**

In 1901, Jokichi Takamine first extracted epinephrine from the adrenal glands of animals and in 1904, Friederich Stolz first synthesized it<sup>6</sup>. Epinephrine is a naturally made hormone created by the adrenal medulla in the adrenal glands. In response to stressful stimuli, the hypothalamus stimulates the pituitary gland which then produces corticotrophin hormones that are sent to the adrenal glands to produce the corticosteroid hormones (epinephrine and norepinephrine).

Specific enzyme-catalyzed reactions that occur in the chromaffin granules of the secretory tissue—epinephrine synthesis<sup>7</sup>:



### **Specific Uses:**

Epinephrine is a medically used drug. For the most part, it is used to stimulate heartbeat and to treat emphysema, bronchitis, bronchial asthma and other allergic conditions, as well as in the treatment of the eye disease, glaucoma.<sup>8</sup> Recently, in hair transplant surgeries, by using its vasoconstrictive properties, epinephrine has been found to aid surgeons by decreasing the existence of intra-operative bleeding.<sup>9</sup>

Naturally, epinephrine is released at an excess amount when the host is faced with stress. This heightening of adrenaline levels in the bloodstream causes the “fight or flight” response of the sympathetic nervous

<sup>2</sup> Safety date for (-)-epinephrine [http://physchem.ox.ac.uk/MSDS/EP/\(-\)-epinephrine.html](http://physchem.ox.ac.uk/MSDS/EP/(-)-epinephrine.html)

<sup>3</sup> “Catecholamine.” The Columbia Encyclopedia, Sixth Edition. 2001

<sup>4</sup> Safety date for (-)-epinephrine [http://physchem.ox.ac.uk/MSDS/EP/\(-\)-epinephrine.html](http://physchem.ox.ac.uk/MSDS/EP/(-)-epinephrine.html)

<sup>5</sup> Duff, Jason (2000). “Adrenaline.” Survey of Organic Chemistry Molecule Projects.

<http://www.chem.vt.edu/chem-dept/helm/2514/project00/adrenaline/adrenaline.html>

<sup>6</sup> “Epinephrine.” The Columbia Encyclopedia, Sixth Edition. 2001

<sup>7</sup> “Hormone” (2000). Encyclopedia Britannica Online. 7/6/01

[http://search.eb.com/bol/topic?eu=120218&sctn=15#s\\_top](http://search.eb.com/bol/topic?eu=120218&sctn=15#s_top)

<sup>8</sup> “Epinephrine.” The Columbia Encyclopedia, Sixth Edition. 2001

<sup>9</sup> “Limiting Epinephrine in Large Hair Transplant Sessions.” Hair Transplant Forum International 2000

[http://www.newhair.com/medical\\_publications](http://www.newhair.com/medical_publications)

system. As a result, there is an increase in heart rate, forced heart contractions, blood flow facilitated to the muscles and brain, relaxation of smooth muscle, and increased aid for the conversion of glycogen to glucose in the liver.<sup>10</sup>

**Action:**

Internally, epinephrine stimulates alpha-, beta1-, and beta2-adrenergic receptors in a dose-related fashion. Epinephrine acts by increasing the levels of cyclic AMP leading to bronchodilation and stimulation of the heart and central nervous system. The drug is often administered through oral inhalation to prevent wheezing and difficulty in breathing<sup>11</sup>

Immediately after epinephrine intake, there is a modest rise in systolic pressure (arteries constrict) which is the result of direct cardiac stimulation and increase in cardiac output. It relaxes the smooth muscles of the bronchi and iris and is a natural antagonist of histamine. In the liver, the drug also produces an increase in blood sugar and glycogenolysis.<sup>12</sup>

Because epinephrine is a hormone, attaching to certain receptor sites on specific cells, it is never internalized into the cell<sup>13</sup> and is therefore quickly inactivated in the body primarily by enzymatic transformation to metanephrine or normetanephrine, which are both excreted in the urine as sulfates and glucuronides.<sup>14</sup> Whether injected or created naturally within the host, epinephrine, the key stimulant of the sympathetic (“fright or flight”) nervous system, does not have a long life once released into the blood stream. Adrenalin (drug form of epinephrine) is said to last for a maximum of 10 minutes once administered.<sup>15</sup> The parasympathetic nervous system counteracts the sympathetic and returns the body back to homeostasis, breaking down excess epinephrine and combining it with the excrement released outside the body.

**Combinations:**

Epinephrine is handled by itself in its natural form, whether extracted or synthesized. It is rarely combined with anything else and more than likely should not be combined with other drugs.<sup>16</sup>

**Status****Historic Use by Organic Farmers:**

Cattle, sheep, horses, and swine many times suffer from anaphylactic reactions in response to the injection of antibiotics, bacterins, and vaccines. Because there are adequate directions for the use of these antibiotics, bacterins, and vaccines, livestock producers are allowed to administer these drugs. Epinephrine injections have proven effective against the onset of anaphylactic shock in animals.<sup>17</sup>

Thorough research has led to a better understanding of the beta-adrenergic receptors (beta-AR). They are present on almost every type of mammalian cell and are stimulated by the neurotransmitter, norepinephrine, and the hormone, epinephrine. It has been discovered that oral administration of some beta-AR agonists (i.e. epinephrine) increases muscle and decreases fat accretion in cattle, pigs, poultry, and sheep.<sup>18</sup>

<sup>10</sup> “Epinephrine.” [Encyclopedia.com](http://www.encyclopedia.com), 7/6/01 <http://www.encyclopedia.com/articles/04158.html>

<sup>11</sup> “Catecholamine.” The Columbia Encyclopedia, Sixth Edition. 2001

<sup>12</sup> “Epinephrine (ADRENALIN).” <http://eilat.sci.brooklyn.cuny.edu/newnyc/DRUGS/EPINEPHR.HTM>

<sup>13</sup> “G Protein Receptors” <http://esg-www.mit.edu:8001/esbio/cb/membranes/gp.html>

<sup>14</sup> “Epinephrine and Norepinephrine” [Encyclopedia Britannica](http://www.britannica.com/eb/article?eu=33378).

<http://www.britannica.com/eb/article?eu=33378>>

<sup>15</sup> “Epinephrine (ADRENALIN).” <http://eilat.sci.brooklyn.cuny.edu/newnyc/DRUGS/EPINEPHR.HTM>

<sup>16</sup> “Epinephrine.” The Columbia Encyclopedia, Sixth Edition. 2001

<sup>17</sup> *Epinephrine Injection 1:1,000 in 10-milliliter containers for emergency treatment.* [Code of Federal Regulations](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/ShowCFR.cfm?FR=500.65). <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/ShowCFR.cfm?FR=500.65>

<sup>18</sup> “Overview of the effects of beta-adrenergic receptor agonists on animal growth including mechanisms of action.” [Journal of Animal Science](http://www.sciencedirect.com/science). <http://www.sciencedirect.com/science>

**OFPA, USDA Final Rule:**

OFPA states in Sec. 6509(c)

“Practices: For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm

- 3) shall not use growth promoters and hormones on such livestock, whether implanted, ingested, or injected, including antibiotics and synthetic trace elements used to stimulate growth or production of such livestock.”<sup>19</sup>

Epinephrine is a naturally secreted hormone, created by the body itself, in response to high stress. Regardless of the situation in which the injection should be administered, the final rule as stated above blatantly refuses the use of hormones.

Policies from the FDA:

*Note:* The following law pertains directly to the legal use of epinephrine in animals.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 500--GENERAL--Table of Contents

Subpart D--Requirements for Specific Animal Drugs

Sec. 500.65 Epinephrine injection 1:1,000 in 10-milliliter containers for emergency treatment of anaphylactoid shock in cattle, horses, sheep, and swine.

(a) Anaphylactoid reactions in cattle, horses, sheep, and swine occur occasionally from the injection of antibiotics, bacterins, and vaccines. Adequate directions for use of these antibiotics, bacterins, and vaccines can generally be written for use by the laity and thus are available to livestock producers. Epinephrine injection is effective for the treatment of anaphylactoid reactions in animals and would be of value in saving lives of animals if it were readily available at the time of administration of the causative agents. In connection with this problem the Food and Drug Administration has obtained the views of the Advisory Committee on Veterinary Medicine, and other experts, and has concluded that adequate directions for over-the-counter sale of epinephrine injection 1:1,000 can be prepared.

(b) In view of the above, the Commissioner of Food and Drugs has concluded that it is in the public interest to make epinephrine injection 1:1,000 available for sale without a prescription provided that it is packaged in vials not exceeding 10 milliliters and its label bears, in addition to other required information, the following statements in a prominent and conspicuous manner: ``For emergency use only in treating anaphylactoid shock. Usual Dosage: Cattle, horses, sheep, and swine—1 cubic centimeter per 100 pounds of body weight. Inject subcutaneously''.

(c) The labeling must also bear a description of the symptoms of anaphylactoid shock including glassy eyes, increased salivation, grinding of the teeth, rapid breathing, muscular tremors, staggering

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<sup>19</sup> 6509 *Animal Production Practices and Materials*. Federal Organic Food Production Act of 1990.  
<http://www.ams.usda.gov/nop/orgact/htm>

gait, and collapse with death following. These symptoms may appear shortly after injection of a bacterin, vaccine, or antibiotic.

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*Note:* The following law pertains to the legal dosage of epinephrine for animals. Relevant information regarding cattle has been highlighted below.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 522--IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS--  
Table of Contents

Sec.522.1258: Lidocaine injection with epinephrine.

(a) Specifications. Each milliliter of the drug contains 20 milligrams (2 percent) of lidocaine hydrochloride, 0.01 milligram of epinephrine, with sodium chloride, and with methylparaben as a preservative, in water for injection.

(b) Sponsor. See No. 000402 in Sec. 510.600(c) of this chapter.

(c) Conditions of use \1\--(1) Amount. The drug is administered by injection as a 2 percent solution or diluted with bacteriostatic water for injection to a 0.5 percent solution for local anesthesia of large and small animals, as follows:

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\1\ These conditions are National Academy of Science/National Research Council reviewed and deemed effective for this drug. Applications for these uses need not include effectiveness data as specified by Sec. 514.111 of this chapter, but may require bioequivalency and safety information.

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(i) Cats: Administer approximately 2 milliliters of 2 percent solution with epinephrine by caudal injection.

***(ii) Cattle: Administer 5 milliliters of 2 percent solution with epinephrine by epidural injection (standing animal). Administer 10 to 20 milliliters of 2 percent solution with epinephrine by cornual nerve block injection. For teat operations and infiltration, inject 0.5 percent solution with epinephrine to effect.***

(iii) Dogs: Administer 2 to 10 milliliters of 2 percent solution with epinephrine by caudal injection. Do not give intravascularly. For infiltration, administer 0.5 percent solution with epinephrine to effect.

(iv) Horses: Administer 5 to 10 milliliters of 2 percent solution with epinephrine by volar nerve block. Administer 10 to 15 milliliters of 2 percent solution with epinephrine by epidural injection. For standing animal, apply slowly and observe individual sensitivity. For infiltration, administer 0.5 percent solution with epinephrine to effect.

(2) Limitations. (i) The drug is contraindicated in the presence of sepsis in the region of proposed injection, shock and heart block, neurologic disease, spinal deformities, septicemia, and hypertension.

- (ii) Do not give intravascularly.
- (iii) Federal law restricts this drug to use by or on the order of a licensed veterinarian.

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*Note:* Relevant statement directly regarding epinephrine regulations are bolded and italicized within the original context.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 500--GENERAL--Table of Contents

Subpart C--Animal Drug Labeling Requirements

Sec. 500.55 Exemption from certain drug-labeling requirements.

(a) Section 201.105(c) of this chapter provides that in the case of certain drugs for which directions, hazards, warnings, and use information are commonly known to practitioners licensed by law, such information may be omitted from the dispensing package. Under this proviso, the Commissioner of Food and Drugs will offer an opinion, upon written request, stating reasonable grounds therefore on a proposal to omit such information from the dispensing package.

(b) The Commissioner of Food and Drugs has considered submitted material covering a number of drug products and has offered the opinion that the following drugs when intended for those veterinary uses for which they are now generally employed by the veterinary medical profession, should be exempt from the requirements of Sec. 201.105(c) of this chapter, provided that they meet the conditions prescribed in this paragraph. Preparations that are not in dosage unit form (for example, solutions) will be regarded as meeting the conditions with respect to the maximum quantity of drug per dosage unit if they are prepared in a manner that enables accurate and ready administration of a quantity of drug not in excess of the stated maximum per dosage unit:

Atropine sulfate. As an injectable for cattle, goats, horses, pigs, and sheep, not in excess of 15 milligrams per dosage unit; as an injectable for cats and dogs, not in excess of 0.6 milligram per dosage unit.

Barbital sodium. For oral use in cats and dogs, not in excess of 300 milligrams per dosage unit.

***Epinephrine injection. 1:1,000. For cats, dogs, cattle, goats, horses, pigs, and sheep (except as provided in Sec. 500.65).***

Morphine sulfate. As an injectable for dogs, not in excess of 15 milligrams per dosage unit.

Pentobarbital sodium. For oral use in cats and dogs, not in excess of 100 milligrams per dosage unit.

Phenobarbital sodium. For oral use in cats and dogs, not in excess of 100 milligrams per dosage unit.

Procaine hydrochloride injection. Containing not in excess of 2 percent procaine hydrochloride, with or without epinephrine up to a concentration of 1:50,000. For use in cats, dogs, cattle, goats, horses, pigs, and sheep.

Thyroid. For oral use in dogs, not in excess of 60 milligrams per dosage unit.

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*Note:* The following law is in reference to the legal human dosage of epinephrine as well as certain required labeling instructions for the storage of the drug. Directly relevant statements are bolded and italicized within original context.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--Continued

PART 341--COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE--Table of Contents

Subpart C--Labeling

Sec. 341.76 Labeling of bronchodilator drug products.

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as a ``bronchodilator.''

(b) Indications. The labeling of the product states, under the heading ``Indications,''' the phrase listed in paragraph (b)(1) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in Sec. 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ``For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma.''

(2) In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain one or more of the following statements:

(i) ``For the'' (select one of the following: ``temporary relief'' or ``symptomatic control'') ``of bronchial asthma.''

(ii) ``Eases breathing for asthma patients'' (which may be followed by: ``by reducing spasms of bronchial muscles'').

(c) Warnings. The labeling of the product contains the following warnings under the heading ``Warnings'':

(1) ``Do not use this product unless a diagnosis of asthma has been made by a doctor.''

(2) ``Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor.''

(3) ``Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a doctor.''

(4) Drug interaction precaution. ``Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not

know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.'

(5) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in Sec. 341.16 (a), (b), (c), and (f).

(i) ``Do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse.'

(ii) ``Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor.'

***(6) For products containing epinephrine, epinephrine bitartrate, or epinephrine hydrochloride identified in Sec. 341.16 (d), (e), & (g).***

***(i) ``Do not use this product more frequently or at higher doses than recommended unless directed by a doctor. [first sentence in boldface type] Excessive use may cause nervousness and rapid heart beat, and, possibly, adverse effects on the heart.'***

***(ii) ``Do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse.'*** (sentence in bold-faced type)

***(iii) For products intended for use in a hand-held rubber bulb nebulizer. ``Do not use this product if it is brown in color or cloudy.'***

(d) Directions. The labeling of the product contains the following information under the heading ``Directions'':

(1) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in Sec. 341.16 (a), (b), (c), and (f). Adults and children 12 years of age and over: Oral dosage is 12.5 to 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Do not exceed recommended dose unless directed by a doctor. Children under 12 years of age: Consult a doctor.

***(2) For products containing epinephrine, epinephrine bitartrate, and epinephrine hydrochloride identified in Sec. 341.16(d), (e), and (g) for use in a hand-held rubber bulb nebulizer. The ingredient is used in an aqueous solution at a concentration equivalent to 1 percent epinephrine. Inhalation dosage for adults, children 12 years of age and over, and children 4 to under 12 years of age: 1 to 3 inhalations not more often than every 3 hours. The use of this product by children should be supervised by an adult. Children under 4 years of age: Consult a doctor.***

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*Note:* The following law pertains to how epinephrine can be sold over the counter without a prescription requirement. Relevant information has been highlighted (bold and italics).

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--Continued

PART 329--HABIT-FORMING DRUGS--Table of Contents

Subpart C--Exemptions



Sec. 329.20 Exemption of certain habit-forming drugs from prescription requirements.

The prescription-dispensing requirements of section 503(b)(1)(A) of the act are not necessary for the protection of the public health with respect to the following drugs subject to section 502(d):

(a) The following exempt narcotic preparations:

(1) Pharmaceutical preparations containing not more than 100 milligrams of opium per 100 milliliters or per 100 grams.

(2) Pharmaceutical preparations containing not more than 16.2 milligrams ( $\frac{1}{4}$  grain) morphine, or any of its salts, per 29.5729 cubic centimeters (1 fluid ounce) or per 28.3 grams (1 avoirdupois ounce);

(3) Pharmaceutical preparations containing not more than 64.8 milligrams (1 grain) codeine, or any of its salts, per 29.5729 cubic centimeters (1 fluid ounce) or per 28.3 grams (1 avoirdupois ounce);

(4) Pharmaceutical preparations containing not more than 32.4 milligrams ( $\frac{1}{2}$  grain) dihydrocodeine, or any of its salts, per 29.5729 cubic centimeters (1 fluid ounce) or per 28.3 grams (1 avoirdupois ounce);

(5) Pharmaceutical preparations containing not more than 16.2 milligrams ( $\frac{1}{4}$  grain) ethylmorphine, or any of its salts, per 29.5729 cubic centimeters (1 fluid ounce) or per 28.3 grams (1 avoirdupois ounce);

Provided, that the preparations described in this paragraph contain one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the preparation valuable medicinal qualities other than those possessed by the narcotic drug alone.

(b) Drugs containing chlorobutanol, intended for external use only.

**(c) Epinephrine solution, 1 percent, preserved with chlorobutanol and intended for use solely as a spray.**

(d) Combination drugs listed in part 329 as exempted from section 511 of the act.

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*Note:* The following law describes the certain regulations that must be followed regarding packaging and labeling of epinephrine. Pertinent lines of information have been highlighted.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 201--LABELING--Table of Contents

Subpart A--General Labeling Provisions

Sec. 201.22 Prescription drugs containing sulfites; required warning statements.

(a) Sulfites are chemical substances that are added to certain drug products to inhibit the oxidation of the active drug ingredient.

Oxidation of the active drug ingredient may result in instability and a loss of potency of the drug product. Examples of specific sulfites used to inhibit this oxidation process include sodium bisulfite, sodium metabisulfite, sodium sulfite, potassium bisulfite, and potassium metabisulfite. Recent studies have demonstrated that sulfites may cause allergic-type reactions in certain susceptible persons, especially asthmatics. The labeling for any prescription drug product to which sulfites have been added as an inactive ingredient, regardless of the amount added, must bear the warning specified in paragraph (b) or (c) of this section.

(b) The labeling required by Secs. 201.57 and 201.100(d) for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement ``Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.'' This statement shall appear in the ``Warnings'' section of the labeling.

***(c) The labeling required by Secs. 201.57 and 201.100(d) for sulfite-containing epinephrine for injection for use in allergic emergency situations shall bear the warning statement ``Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.'' This statement shall appear in the ``Warnings'' section of the labeling.***

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*Note:* The following law pertains to the regulations regarding the storage of epinephrine in self-pressurized aerosol cans. Pertinent lines of information have been highlighted.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 2--GENERAL ADMINISTRATIVE RULINGS AND DECISIONS--Table of Contents

Subpart G--Provisions Applicable to Specific Products Subject to the Federal Food, Drug, and Cosmetic Act

Sec. 2.125 Use of chlorofluorocarbon propellants in self-pressurized containers.

(a) As used in this section:

(1) Chlorofluorocarbon means any fully halogenated chlorofluoroalkane.

(2) Propellant means a liquefied or compressed gas that is used in

whole or in part to expel from the same self-pressurized container or from a separate container a liquid or solid material different from the propellant, but the term does not include the use of a chlorofluorocarbon as an aerating agent for foamed or sprayed food products.

(b) Chlorofluorocarbons are widely used in products subject to the Federal Food, Drug, and Cosmetic Act, with the principal use being as propellants in self-pressurized containers. Information recently developed indicates that chlorofluorocarbons may reduce the amount of ozone in the stratosphere and thus increase the amount of ultraviolet radiation reaching the earth. An increase in ultraviolet radiation may increase the incidence of skin cancer, change the climate, and produce other effects of unknown magnitude on humans, animals, and plants. Chlorofluorocarbons may also affect the climate by increasing infrared absorption in the atmosphere.

(c) Except as provided in paragraph (e) of this section, any food, drug, device, or cosmetic in a self-pressurized container that contains a chlorofluorocarbon propellant is adulterated and/or misbranded in violation of the act, and any drug product in a self-pressurized container that contains a chlorofluorocarbon propellant is a new drug or a new animal drug.

(d) The use of a chlorofluorocarbon as a propellant in a self-pressurized container of a drug product will not result in the drug product being adulterated and/or misbranded provided a new drug application, a new animal drug application, or in the case of a certifiable antibiotic an antibiotic application for the drug product has been approved, a petition has been filed as provided by paragraph (f) of this section, and paragraph (e) of this section has been amended to specify the use as essential.

(e) The adulteration and misbranding provisions of paragraph (c) of this section shall not apply to the following essential uses of chlorofluorocarbons:

- (1) Metered-dose steroid human drugs for nasal inhalation,
- (2) Metered-dose steroid human drugs for oral inhalation,
- (3) Metered-dose adrenergic bronchodilator human drugs for oral inhalation,
- (4) Contraceptive vaginal foams for human use, and
- (5) Metered-dose ergotamine tartrate drug products administered by oral inhalation for use in humans.
- (6) Intrarectal hydrocortisone acetate for human use.
- (7) Polymyxin B sulfate-bacitracin zinc-neomycin sulfate soluble antibiotic powder without excipients, for topical use on humans.
- (8) Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application.
- (9) Metered-dose nitroglycerin human drugs administered to the oral cavity.
- (10) Metered-dose cromolyn sodium human drugs administered by oral inhalation.
- (11) Metered-dose ipratropium bromide for oral inhalation.
- (12) Metered-dose atropine sulfate aerosol human drugs administered by oral inhalation.
- (13) Metered-dose nedocromil sodium human drugs administered by oral inhalation.
- (14) Metered-dosed ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use.
- (15) Sterile aerosol talc administered intrapleurally by thoracoscopy for human use.

(f) Any person may file a petition in accordance with part 10 of this chapter to amend paragraph (e) of this section to specify a use of chlorofluorocarbons in a product as not being subject to the adulteration and misbranding provisions in paragraph (c) of this section. The petition must be supported by an adequate showing that:

(1) There are no technically feasible alternatives to the use of a chlorofluorocarbon in the product,

(2) The product provides a substantial health benefit, environmental benefit, or other public benefit that would not be obtainable without the use of the chlorofluorocarbon, and

(3) The use does not involve a significant release of chlorofluorocarbons into the atmosphere or that the release is warranted in view of the consequence if the use were not permitted.

(g) Any holder of an approved new drug application or new animal drug application for a drug product containing a chlorofluorocarbon in a self-pressurized container, except those drug products listed in paragraph (e) of this section, shall submit to the Food and Drug Administration on or before October 1, 1978, either a supplemental application providing for a revised formulation complying with the requirements of Sec. 314.70 or Sec. 514.8 of this chapter or a letter requesting that a new drug application or a new animal drug application for the drug product containing chlorofluorocarbon be withdrawn and that the right to a hearing on the withdrawal of the application is waived.

(h)(1) Each manufacturer of a drug product listed in paragraph (e) of this section that is not covered by an approved new drug application shall submit a new drug application in accord with Sec. 314.50 of this chapter on or before June 15, 1978.

(2) An abbreviated new drug application conforming to Sec. 314.94 of this chapter is acceptable in lieu of a full new drug application for any product included in the classes of products in paragraph (e) of this section if the product is one that is described under Sec. 314.92 of this chapter. A finding has been made that an abbreviated new drug application may be submitted for the following products included in the classes of products listed in paragraph (e) of this section:

(i) Ergotamine tartrate supplied in a metered-dose aerosol form suitable for oral inhalation for the treatment of migraine headaches. Each measured dose must deliver a dose of the active ingredient equivalent to that contained in the product that has been the subject of a separate finding that an abbreviated new drug application is suitable.

(ii) Isoproterenol hydrochloride supplied in a metered-dose aerosol form suitable for oral inhalation for use as an adrenergic bronchodilator. Each measured dose must deliver a dose of the active ingredient equivalent to that contained in the products that have been the subject of a separate finding that an abbreviated new drug application is suitable.

**(iii) Epinephrine, epinephrine bitartrate, or epinephrine hydrochloride (racemic) in a metered-dose aerosol form suitable for oral inhalation for use as an adrenergic bronchodilator. Each measured dose must deliver a dose of the active ingredient equivalent to that specified in an OTC proposed or final monograph issued under the provisions of 21 CFR part 330.**

(iv) Nonoxynol 9 in an aerosol foam suitable for vaginal administration as a contraceptive foam. The aerosol foam must contain 8 to 12.5 percent of nonoxynol 9.

(i) Any sponsor of an ``Investigational New Drug Application'' (IND) or ``Notice of Claimed Exemption for a New Animal Drug'' (INAD) for a drug product containing a chlorofluorocarbon shall:

(1) Amend the IND or INAD on or before December 15, 1978, to revise the formulation removing the chlorofluorocarbon.

(2) Submit the information required under paragraph (f) of this section to amend paragraph (e) of this section to show that the use of chlorofluorocarbon is essential, or

(3) Submit the information required under paragraph (j) of this section requesting that studies with the drug product containing a chlorofluorocarbon propellant be allowed to be performed.

(j) Any sponsor of an IND or INAD who wishes to initiate or continue a study beyond December 15, 1978 on a drug product containing a chlorofluorocarbon shall submit a petition in accordance with part 10 of this chapter requesting that studies be permitted to collect the data to show that the use of the chlorofluorocarbon is an essential use. The petitions must be supported by the following:

(1) A description of the drug product,

(2) An explanation why a chlorofluorocarbon propellant is used in the product rather than another propellant or another dosage form of the product, and

(3) The benefit that the investigational product is believed to have and that the sponsor hopes to demonstrate by the studies.

(k) The Commissioner will initiate action to withdraw approval of an application or terminate an IND or INAD notice in accordance with the applicable provisions of section 505 of the act and parts 312 and 314 of this chapter, or section 512 of the act and parts 511 and 514 of this chapter upon failure of a holder of an approved new drug application or approved new animal drug application or sponsor of an IND or INAD notice to comply with the applicable provisions of this section.

(1) Food, drug, device, or cosmetic products manufactured or packaged on or after December 15, 1978, and finished products initially introduced into interstate commerce on or after April 15, 1979, shall comply with this regulation.<sup>20</sup>

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#### **Regulatory: EPA/NIEHS/Other Sources**

EPA: In 1988, epinephrine was listed as a Class IV Hazardous Organic Compound based on the UDRI Thermal Stability-Based Incinerability Ranking.<sup>21</sup>

A more recent case proved inconclusive about the hazardous effects of epinephrine: when 200,000 ppm of the hormone was administered to dogs, induced arrhythmia was reported. However, when tested with 50,000 ppm of epinephrine, there was no induced arrhythmia reported. In both cases, the amount injected was at a much greater concentration than that which the body creates (normal human plasma concentration of epinephrine is less than 140 pg/mL) and therefore proved inconclusive.<sup>22</sup>

OSHA: none

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<sup>20</sup> All above laws regarding epinephrine and its legal use were directly copied and pasted from the government archives found on the web under relevant sections that pertained to this research. No alterations were made except certain significant information within the original text was highlighted for convenience purposes as previously noted. <http://www.accessdata.fda.gov/scripts>

<sup>21</sup> Appendix 4. UDRI Thermal Stability-Based Incinerability Ranking. *Hazardous Organic Compound Ranking*. <http://yosemite.epa.gov/osw.rcra.nsf/documents/CA8C9D5BE98F3D7F852565DA006F0597>

<sup>22</sup> IRIS Summary – Pentafluoroethane <http://www.epa.gov/iris/subst/0683.htm>

NIOSH: People and animals exposed to high CFC-113 and other CFC contents have serious reactions to drugs containing epinephrine and norepinephrine. NIOSH feels that EMTs should be aware of this prior to treating patients who might have been highly exposed.<sup>23</sup>

ACGIH: none

NTP, IARC: not listed as a known carcinogen.<sup>24</sup>

NOSB: Epinephrine material is scheduled to be petitioned in September of 2002.

Category: Livestock

Petitioned use of material: Hormone for Anaphylactic reactions; anaphylaxis

NIEHS: Chapter 5 of the NIEHS Health and Safety Manual describes the regulations regarding "acutely toxic chemical." Epinephrine is listed by regulations as a chemical which requires special handling. The containers which it is stored in should not be rinsed out but must be presented to the Health and Safety Branch for proper handling.<sup>25</sup>

FAAN: Food Allergy and Anaphylaxis Network has epinephrine FDA approved for use by Emergency Medical Technicians in May 2002.

### **Status Among U.S. Certifiers**

NOFA: "The following medications are allowed with a 5 day withholding:

- non-steroidal anti-inflammatory (i.e. banamine)
- antihistamines (e.g. epinephrine, adrenaline)
- anesthetics"<sup>26</sup>

### **State Organic Certifiers:**

Ohio: Since epinephrine is an enzyme it is allowed in its pure and non-synthetic form.

It is allowed in feed additives in its natural form as long as it is derived from a non-pathogenic host<sup>27</sup>

Colorado/Rhode Island: do not certify for livestock

Texas: not listed in database

Pennsylvania: OMRI recognizes that the inclusion is contradictory to a general prohibition on hormones. OMRI believes that a hormone could be included on the National List and administered to an organic animal as long as it (1) is included on the National List, (2) is not administered in the absence of disease, and (3) is not used with the purpose of stimulating growth or production.<sup>28</sup>

### **International**

IFOAM Basic Standards 2000: Section 5.7.3c forbids the use of hormones for heat induction and heat synchronization unless used for an individual animal against reproductive disorders, justified by veterinary indications. Section 6.6.4 states that the use of synthetic hormones and synthetic growth promoters are not allowed.<sup>29</sup>

EU: prohibits the use of hormones.

Canadian General Standards: Canada possesses 3 standards of beef—natural beef, certified organic beef, and certified hormone-free beef<sup>30</sup>

## **Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria**

<sup>23</sup> DHHS (NIOSH) Publication No. 89-109: <http://www.cdc.gov/niosh/89-109.html>

<sup>24</sup> Chemical Hygiene Plan, Appendix C: *Carcinogens*  
<http://www.chem.pacificu.edu/ChemHyg&Invent/CHP/CHP%20App%20C%20Carcinogens.html>

<sup>25</sup> "What Are Chemical Wastes?" <http://www.niehs.nih.gov/odhsb/wasteman/chemical/whatis.htm>

<sup>26</sup> VOF Organic Meat & Egg Production – NOFA Vermont [http://www.nofavt.org/sht02\\_stds7.cfm](http://www.nofavt.org/sht02_stds7.cfm)

<sup>27</sup> Sears, Steve: Administrator of Ohio Ecological Farm and Food Association. Telephone Interview. Tuesday, June 4, 2002.

<sup>28</sup> Information provided by OMRI [http://www.omri.org/OMRI\\_TAP\\_2002.html](http://www.omri.org/OMRI_TAP_2002.html)

<sup>29</sup> IFOAM Basic Standards <http://www.ifoam.org/standard/basics.html#10>

<sup>30</sup> Canada Beef Export Federation February 2001 [http://www.agric.gov.ab.ca/agdex/400/420\\_830-3.pdf](http://www.agric.gov.ab.ca/agdex/400/420_830-3.pdf)

1. *The potential of the substance for detrimental interactions with other materials used in organic farming systems.*

Epinephrine has not been proven to interact with many other materials used in organic farming systems but it has been monitored from a medical perspective regarding the harmful effects that occur from combinations with other drugs:

**With monoamine oxidase (MAO) inhibitors:** epinephrine's general effects may be potentiated.

**With other sympathomimetic drugs (i.e. isoproterenol):** possible additive effects and increased toxicity within the patient.

**With cyclopropane, halothal, isoprenaline and other halogenated hydrocarbon anesthetics:** cardiac arrhythmia may be induced.

**Used along with diuretic agents:** may decrease vascular response to epinephrine

**With guanethidine:** epinephrine antagonizes the neuron blockade that guanethidine is responsible for, thus decreasing the antihypersensitive effect and requiring a greater dosage of guanethidine.<sup>31</sup>

**When used with alpha-blockers:** reduced blood pressure.

**With beta blockers:** bradycardia, sometimes paradoxical elevation of blood pressure.

**With phenothiazine and saluretics:** actions of epinephrine are reduced.

**With thyroid hormones:** epinephrine actions are enhanced.

2. *The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.*

**Toxicity:**

The laevo-rotary form of epinephrine, (-)-epinephrine, has been declared highly toxic and can be fatal if inhaled, swallowed, or absorbed through the skin. It may also cause harm or be fatal to the unborn child and can potentially cause reproductive defects.

According to the UN Hazard Codes, (-)-epinephrine (UN No. 2811) is listed as a Packing Group II, Major Hazard Class 6.1.<sup>32</sup>

Epinephrine has a storage lifetime of about 2 years and recently, the FDA was forced to issue a recall for some vials of the hormone that were near or past its expiration date:

August 19, 1999

**URGENT DRUG RECALL Subpotency**

PRODUCT: Epinephrine Injection, USP 1:1000 1 mg/mL Tubex

SIZE: 1 mL Tubex, 10 Tubex per box

NDC: 0008-0263-01

LOT NOS: 2971529 (EXP 11/99); 2971530 (EXP 9/99)  
2971534 (EXP 2/00); 2971535 (EXP 3/00)  
2971536 (EXP 4/00. 2971538 (EXP 5/00)  
2983265 (EXP 7/00)

DISTRIBUTION: June 1997- February 1999

<sup>31</sup> "Epinephrine (ADRENALIN)." <http://eilat.sci.brooklyn.cuny.edu/newnyc/DRUGS/EPINEPHR.HTM>

<sup>32</sup> Safety date for (-)-epinephrine [http://physchem.ox.ac.uk/MSDS/EP/\(-\)-epinephrine.html](http://physchem.ox.ac.uk/MSDS/EP/(-)-epinephrine.html)

TO: Wyeth-Ayerst Customers

Wyeth-Ayerst is voluntarily recalling specific lots of Epinephrine Injection, USP 1:1000 in 1 mg/mL Tubex(g). We have observed discolored samples in our finished product stability program. A few of these samples have been found to be subpotent at or near expiration, which may suggest a potential health hazard. You should extend this recall to the hospital pharmacy and physician shelf level.

Please examine your inventory of Epinephrine Injection, USP 1: 1000 in 1 mg/mL Tubex immediately, and follow the appropriate course of action described below.

1. If you have any of the seven lots listed above, please remove them immediately from sale or use and return all of the above-listed lot numbers to the following location:

Wyeth-Ayerst Laboratories  
Dock 27  
31 Morehall Road  
Frazer, Pennsylvania 19355  
Attn. V. Murray

Please complete the enclosed packing slip and include it with your return to ensure proper credit. Please use the enclosed shipping label for ease of handling. You will receive credit for the returned merchandise and you will be reimbursed for the shipping charges.

2. If you have distributed any of these specific lots to subordinate accounts, please notify them of this recall immediately and request return of the products to you for your consolidated return to us, recall is to be extended to all retail/dispensing, hospital, and physician accounts.
3. Please mark the appropriate box or boxes on the enclosed pre-paid postcard, record the quantity you will return, and send the postcard to us as soon as possible. Your response, even if YOU do not have nay recalled product from the subject lots is very important to both us and the FDA in monitoring the effectiveness of this recall.

The Food and Drug Administration has full knowledge of this recall. Wyeth-Ayerst apologizes for any inconvenience resulting from this recall. If you have any questions, please call our Product Quality Department at 1-800-999-9384. Thank you for your cooperation.

Sincerely yours,

Anil Sawant, Ph.D.  
Assistant Vice President  
Quality Assurance

\_\_\_\_\_  
Wyeth-Ayerst Laboratories<sup>33</sup>  
\_\_\_\_\_

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**Environmental Effects:**

<sup>33</sup> U.S Food and Drug Association <http://www.fda.gov/medwatch/safety/1999/epinep.htm>



As previously mentioned, the EPA Appendix for Hazardous Waste in 1988 declared epinephrine as a Class IV Hazardous Organic Compound based on the UDRI Thermal Stability-Based Incinerability Ranking. This means that the chemical needs to be handled accordingly and cannot be disposed of by normal means. The rules and regulations regarding care of hazardous waste explains the results of irresponsible care of such compounds.

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

As aforementioned, epinephrine has a shelf life of 2 years. Stored epinephrine that remains preserved for longer than that time is considered hazardous. Otherwise, it is not considered hazardous:

## Fact Sheets and Information Papers

### Epinephrine Management

January 2002

1. BACKGROUND Epinephrine is used pharmaceutically as a cardiac stimulant, and a relaxer to bronchial smooth muscles. It is also called adrenaline. It is found in bee sting kits, spinal anesthesia kits, and is usually administered from 1-2 milliliter prefilled syringes and solutions containing very low concentrations (injection solution of 1:1000 or 1:10,000). Waste or expired shelf life epinephrine as the sole active ingredient in a solution is listed in section 40 CFR 261.33(e) of the Federal Environmental Protection Agency's (EPA) hazardous waste regulations as an acutely hazardous waste. The EPA hazardous waste code is P042. Residual epinephrine in dispensing instruments after use does not meet the criteria of a P042 waste as described below.

#### 2. EPINEPHRINE MANAGEMENT

a. According to a federal EPA clarification published in the December 1994 Monthly Hotline Report as Question No.3, residual epinephrine in a syringe after injection is not a P042 waste. According to the report, drug residues in dispensing instruments are part of the use of the chemical for its intended purpose and are not a hazardous waste unless it exhibits a hazardous waste characteristic. Because the residual epinephrine in the syringe is not listed, and because it does not show the characteristics of a hazardous waste (40 CFR 261.21-261.24), it does not meet the definition of a hazardous waste. Therefore, it is appropriate to discard syringes containing residual epinephrine (e.g. after administering it to patients) into any sharps container.

Off-specification or exceeded shelf-life epinephrine would be considered unsuitable for use on patients and therefore it is inherently waste like. Any stocks that are an unused, sole active ingredient solution, and a commercial product, must be managed as an acutely hazardous waste (EPA hazardous waste code P042). Return of such stocks to the manufacturer is NOT appropriate unless the action is complete before the declaration of unsuitability or the expiration date. The one exception would be that outdated epinephrine may be used for training purposes, locally, without being managed as a hazardous waste.

b. Turn-in Procedures. Stocks supplied by the Prime Vendor mechanism are less likely to become outdated, and are not subject to the discussion that follows. Stocks that are purchased through the Federal Supply System or by local purchase are to be managed as discussed in the following paragraphs.

(1) To the maximum possible extent, end users should identify and return to Logistics any stocks of epinephrine that have not yet, but which soon will reach the expiration date. This action will make it more likely that Logistics can return old but not expired stocks to the manufacturer, either with or without credit.

Any such return is shipped using ordinary practices that are customary for transportation of new product. The hazardous waste requirements do not pertain.

(2) Epinephrine that is off-specification, unserviceable, expired, or otherwise unusable must be turned-in through regular supply channels and managed as a hazardous waste. This pertains to stock where epinephrine is the sole active ingredient. It also pertains to stocks in any type of packaging (preloaded syringes, vials, ampules, etc.). The hazardous waste management actions may vary among various Logistics or Medical Supply activities, but usually will involve any of the following: turn into DRMO, commercial contract with a permitted hazardous waste disposal firm, or other equivalent procedures that are recognized and approved by the environmental office at the supporting military installation.

3. MIXTURES. There are commercial products where epinephrine is an ingredient but not the sole active ingredient. When these products are unserviceable, off-specification, outdated, or used, they are not classified or managed as a hazardous waste [EPA Comment in 40 CFR 261.33d]. Examples include Bupivacaine HCL Epinephrine, Lidocaine and Epinephrine, and Prilocaine and Epinephrine. Such mixtures can be returned to the manufacturer if arrangements can be made, or they can be destroyed using the disposal guidance in the Military Item Disposal Instructions (MIDI).<sup>34</sup>

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4. *The effects of the substance on human health.*

The following is based on the findings of the epinephrine drug used on humans requiring medical attention.

**Epinephrine Indications:**

Bronchial asthma  
Acute allergic reaction  
Cardiac arrest  
Asystole  
Electromechanical dissociation  
Ventricular fibrillation unresponsive to initial defibrillatory attempts

**Epinephrine Contraindications:**

Hypersensitivity  
Hypovolemic shock  
Coronary insufficiency  
Hypertension

**Potential Health Effects (2):**

Headache  
Nausea  
Restlessness  
Weakness  
Dysrhythmias  
Hypertension  
Precipitation of angina pectoris  
Safe Use during Pregnancy is questionable (research in process)  
Syncope has occurred after administration to asthmatic children  
May increase myocardial oxygen demand (check website listed).

**How Epinephrine Is Supplied**

Parenteral:

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<sup>34</sup> "Epinephrine Management." Fact Sheets and Information Papers. January 2002. <http://chppm-www.apgea.army.mil/hmwp/Factsheets/EPINEPHRE>

1 mg/ml (1: 1,000), 0.1 mg/ml (1: 10,000) ampule and prefilled syringe  
 Auto-injector (EpiPen) 0.5 mg/ml (1:2,000)  
 0.01 mg/ml (1:100,000) pediatric

### **Epinephrine Dosage and Administration**

#### **Asystole, pulseless electrical activity, or ventricular fibrillation:**

##### *Adult:*

Initial: 1mg IV push, repeat q 3-5 min  
 Intermediate: 2-5 mg IV push q 3-5 min  
 Escalating: 1 mg-3 mg-5 mg IV (3 min apart)  
 High: 0.1 mg/kg IV push q 3-5 min

##### *Pediatric:*

First dose: Standard (0.1 ml/kg 1:10,000) IV/IO  
                   High (0.1 ml/kg 1: 1,000) ET  
                   High (0.1 ml/kg 1: 1,000) IV/VO  
 Second and Subsequent doses: High (0.1 ml/kg 1:1,000) ET

#### **Bradycardia refractory to other interventions**

*Adult:* 2-10 mcg/min (1 mg 1: 1,000 in 500 ml of normal saline or D5W)

*Pediatric:* Standard: 0.1 ml/kg 1: 10,000 IV/IO  
                   High: 0.1 ml/kg 1: 1,000 ET<sup>35</sup>

As long as epinephrine is used in its proper dosage, then there will be no harmful effects of the drug.

In relation to meat production and human health, epinephrine has a very short internal life-span (when injected into the animal), but with regards to how soon after injection is the animal slaughtered, there is a brief abstract from the NIH files that explains what happens:

HEEP COPYRIGHT: BIOL ABS. "Dark-cutting" beef commonly results when **cattle** are subjected to intensive stress prior to slaughter. **Epinephrine** administration s.c. for 24-48 hr prior to slaughter has been shown to mimic the condition produced by natural stress conditions. The beta-adrenergic blockade agent DL-propranolol-HCl has previously been shown to prevent the "dark-cutting" condition when applied to sheep. In this present study, doses of propranolol at 52.8 mg/100 kg and above, administered at 6 intervals over the 44-hr period preceding slaughter, were completely effective in prevention of "dark-cutting" beef as induced by **epinephrine** injection. Propranolol at 17.6 mg/100 kg was marginally effective. Calculations suggest that propranolol in the meat of injected animals would be far below what is considered to be a minimal effective oral dose for human consumption.<sup>36</sup>

It is for this reason that NOFA regulations require a withholding of five days for certainty (as stated earlier).

The following are the orders given to a veterinarian regarding the epinephrine dosage for animal care:

VET: **EPINEPHRINE** INJECTION (1:1000): DO NOT USE IN ACUTE HYPOTENSION PRODUCED BY PHENOTHIAZINE DERIVED TRANQUILIZERS, SINCE FURTHER DEPRESSION OF BLOOD PRESSURE CAN OCCUR. DO NOT USE WHEN CYCLOPROPANE OR HALOGENATED ANESTHETICS ARE USED BECAUSE OF POSSIBLE CARDIAC COLLAPSE. DO NOT USE IN TREATMENT OF VASCULAR SHOCK. DO NOT USE IN PATIENTS KNOWN TO BE SENSITIVE TO **EPINEPHRINE**. ... USE WITH CAUTION IN HYPERTHYROID ANIMALS; ANIMALS BEING TREATED WITH THYROID, DIGITALIS, OR MERCURIAL DIURETICS. DO NOT USE INJECTION IF IT IS BROWN OR CONTAINS A PRECIPITATE.

<sup>35</sup> "Epinephrine (ADRENALIN)." <http://eilat.sci.brooklyn.cuny.edu/newnyc/DRUGS/EPINEPHR.HTM>

<sup>36</sup> Ashmore. Cr. Carroll, F. Doerr, L. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAvHaOZo:4>

[Aronson, C.E. (ed.). *Veterinary Pharmaceuticals & Biologicals*, 1980-1981. Media, Pa.: Harwal Publishing Co., 1980.,p. 16-48]\*\*QC REVIEWED\*\*<sup>37</sup>

5. *The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.*

In relation to meat production and human health, epinephrine has a very short internal life-span (when injected into the animal), but with regards to how soon after injection is the animal slaughtered, there is a brief abstract from the NIH files that explains what happens:

HEEP COPYRIGHT: BIOL ABS. "Dark-cutting" beef commonly results when **cattle** are subjected to intensive stress prior to slaughter. **Epinephrine** administration s.c. for 24-48 hr prior to slaughter has been shown to mimic the condition produced by natural stress conditions. The beta-adrenergic blockade agent DL-propranolol-HCl has previously been shown to prevent the "dark-cutting" condition when applied to sheep. In this present study, doses of propranolol at 52.8 mg/100 kg and above, administered at 6 intervals over the 44-hr period preceding slaughter, were completely effective in prevention of "dark-cutting" beef as induced by **epinephrine** injection. Propranolol at 17.6 mg/100 kg was marginally effective. Calculations suggest that propranolol in the meat of injected animals would be far below what is considered to be a minimal effective oral dose for human consumption.<sup>38</sup>

It is for this reason that NOFA regulations require a withholding of five days for certainty (as stated earlier).

As indicated earlier (see criteria 3), EPA has declared epinephrine a hazardous waste when passed its expiration date and must therefore be monitored appropriately; according to the specific procedures dictated in the Hazardous Waste Laws, expired epinephrine should be handled:

6. *The alternatives to using the substance in terms of practices or other available materials.*

In regards to alternative methods of handling anaphylaxis, the following is an abstract listing a few other possibilities that were discovered in humans<sup>39</sup>

IPA COPYRIGHT: ASHP The absorption of sublingual isoproterenol (isoprenaline; I), 10 mg, given as treatment for severe anaphylactic reactions to insect stings, and at a dose of 2.5-80 mg to control an attack of asthma, is variable and excessive absorption may be dangerous. Syringes containing **epinephrine (adrenaline; II)** should be given to such patients for self-administration and even to patients undergoing prophylactic immunotherapy with bee and wasp venoms since the protective effect of immunotherapy is not absolute. An **alternative** possibility is the inhalation of isoproterenol sulfate in high concentrations (Medihaler-Iso-forte), which may modify the course of acute anaphylaxis and may be used in patients who are not able to self-administer II.

Stopping the occurrence of cardiac arrest in humans and animals has been a recent discovery. Logically, there are only a few remedies as described in the excerpt below:

<sup>37</sup> HSDB: *Epinephrine*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAA8OaWla:1>

<sup>38</sup> Ashmore. Cr. Carroll, F. Doerr, L "Effects of propranolol on characteristics of beef carcasses." <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAvHaOZo:4>

<sup>39</sup> "Sublingual isoprenaline as a treatment for anaphylaxis." <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAcEaOUh:1>

The invention relates to new drugs for augmenting perfusion pressure administered during cardiopulmonary resuscitation and other shock states. The compounds include **phenylethanolamines** and **imidazolines**, and **fluorinated derivatives** thereof, which act on adrenergic receptors in patients. The compounds of the invention enhance neurologic outcome and survival, and decrease ventricular dysrhythmias in patients suffering cardiac arrest and other shock states, relative to the outcomes, survival, and post defibrillation ventricular dysrhythmias in conventional therapy for use in resuscitation.<sup>40</sup>

7. *Its compatibility with a system of sustainable agriculture.*

Epinephrine is not a hazardous material until stored beyond its expiration date in which case, it should be disposed of properly, according to the directions given by the EPA Hazardous Waste Laws. This then is a human error as opposed to a chemical fault.

In its natural state, epinephrine is an enzyme produced by the body itself and used to help physiologically cope with highly stressful situations. In matters of medical attention, such as anaphylaxis or acute allergic reactions, epinephrine seems to be the only available solution. The required dosage for relief of these listed ailments is much less than the dosage required for its affects to be harmful to the patient. Additionally, the life-span of injected epinephrine in the body is much like the life-span of naturally secreted epinephrine and it is broken down within the body and passed as harmless components through the host's urine.

Precautions can be taken by the farmer to ensure that there is ample time between the injection and the slaughter in order to prevent all reasons for concern.

The negative affects of the drug are only encountered when it is misused and given in illegal proportions. These lapses in responsibility can actually lead to very serious consequences including death of not only the needy animal but to others as well. But this is the case with any sort of material. Although there seems to be legitimate cases in which the use of epinephrine can be justified, the EPA final ruling declares that no hormone can be used on livestock.

## **TAP Reviewer Discussion**

**Reviewer 1** [*Director of Programs, Farm Animal & Sustainable Agriculture  
Humane Society of the United States, Northeast*]

Discussion of TAP Review for Epinephrine

Summary of Reviewer's Analysis

- **Despite being a hormone, the medical use is a basic veterinary tool.**
- **Despite being a hormone, epinephrine is used for very specific purposes under medical emergencies.**
- **The residual effect of the drug is very short lived in the animal.**
- **Clarify the specific use of epinephrine in the material list.**
- **Require a withdrawal time for the animal from organic certification for 5 days after epinephrine use.**

For veterinary treatment of livestock medical conditions, Epinephrine has a place in organic animal care. The argument that being a hormone automatically eliminates it from consideration is compelling, however, the definition of hormone "use" needs to be clarified. The pretext for hormones as in "hormone-free" indicates that hormones are used as a matter of routine use such as subtherapeutic dosages. The use of epinephrine for veterinary practice as a recourse for specific condition such as counteracting severe reactions in cattle, horses, sheep, and swine from anaphylactic shock appears to be necessary and consistent with the necessary care of animals in distress.

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<sup>40</sup> The Office for Technology Licensing: "Drugs for the Treatment of Cardiac Arrest and Other Shock States" <http://techpartners.osu.edu/abstracts/94ID28F.html>

The use of epinephrine for veterinary care must be the only use this drug has in organic production. Application and dosage must be followed according to pharmaceutical directions. As OMRI has indicated, a hormone could be included on the National List and administered to an organic animal as long as it (1) is included on the National List, (2) is not administered in the absence of disease and (3) is not used with the purpose of stimulating growth or production.

#### **Reviewer 1 Conclusion**

The literature notes that as long as epinephrine is used in its proper dosage, then there will be no harmful effects of the drug. The benefits far outweigh any types of problems. Since the drug has a very short life span within the body after administration, then no residual problems should occur. However, as mentioned in the TAP review, “dark cutting” of beef or other meats can occur. It is recommended that an animal be withheld from slaughter for five days. Another “side effect” to epinephrine use is increased sweating in the animal as well as increased heart rate and blood pressure. It takes the animal from a few minutes to several hours to return to normal.

#### **Reviewer 1 Recommendation Advised to the NOSB**

To avert fears some people might have concerning any hormone use, and since it would be of benefit in the case of slaughter, I would include that the 5 day withholding period be imposed for any sort of animal production after the use of epinephrine.

**Reviewer 2** [*PhD. Reproductive Physiology. Research, consulting, professor of animal sciences with activities related to animal production. Southeast*]

#### **Summary and Comments**

Because epinephrine stimulates both alpha and beta receptors the following observation on the use of a synthetic agent, clenbuterol, must be taken into account.  $\beta$ -Adrenergic agonists increase growth rate, but their efficacy is reduced over time as the number of  $\beta_2$ -adrenoceptors in muscle decreases. Dexamethasone increases  $\beta_2$ -adrenoceptor density in many tissues, but this effect has not been reported in skeletal muscle. The dexamethasone reference here is to assess what might be happening during stressful situations as dexamethasone is a synthetic cortisol. Dexamethasone caused a marked suppression of growth rate, which resulted in decreased body weight (–29%), carcass weight (–30%), hind-limb muscles (–22%), omental fat (–22%), and heart weight (–10%). Feed intake was reduced (–26%), but feed conversion efficiency was also impaired. Clenbuterol caused a small increase in growth rate (+6%), with an increase in leg muscle (+7%) and heart mass (+8%). Feed efficiency was improved by clenbuterol. Rats given the combined treatment still showed a reduction in growth rate (–81%). Clenbuterol caused a slight increase in the affinity  $\beta_2$ -adrenoceptors in. Relative to control values, the density of  $\beta_2$ -adrenoceptors in lung was +31% with dexamethasone treatment, –45% with clenbuterol, and –23% with the combined treatment. Clenbuterol also decreased  $\beta_2$ -adrenoceptors in skeletal muscle (–35%), but so did dexamethasone (–13%), so the effects of the  $\beta$ -adrenergic agonist were not attenuated through use of the combined treatment (–40%). The results show that the inductive effect of glucocorticoids on  $\beta_2$ -adrenoceptors is tissue-specific and that glucocorticoid treatment is not a useful adjunct to  $\beta$ -adrenergic agonist treatment in animal production. Drugs that activate  $\beta_2$ -adrenoceptors increase muscle growth, but their effects diminish over time, partly because the number of  $\beta_2$ -adrenoceptors in muscle decreases over time. Dexamethasone is a synthetic steroid that increases the number of  $\beta_2$ -adrenoceptors and enhances the effects of  $\beta$ -adrenergic agonists in lung tissue.<sup>b</sup>

The effect of the beta-adrenergic agonist clenbuterol on immune function was examined in sheep. Twenty ewe lambs were housed indoors, with food and water available on an ad libitum basis, and immunized against somatostatin (SRIF) using a SRIF-ovalbumin conjugate. Ten of the lambs were also treated with clenbuterol (400 mg/kg) each day; 10 controls were not treated. After 5 wk of treatment, the lambs were bled and then slaughtered for carcass composition. The lambs that received immunization alone produced significant antibody titers against SRIF, whereas 9 of the 10 clenbuterol treated lambs produced no

significant, specific antibody response. These results indicate that treatment with clenbuterol may inhibit humoral antibody response to infection.<sup>c</sup>

The mechanism through which the repartitioning agent clenbuterol increases heart rate was investigated. First, the relative importance of the B1- and B2-adrenoceptors was established in rat and bovine right atria in vitro. The positive chronotropic and inotropic effects of (+)isoproterenol in rat and bovine right atria, respectively, were markedly antagonized by the B1-adrenoceptor antagonist CGP 20712A but were antagonized less by the B2-adrenoceptor antagonist IC1 118 551 in rat, but not in bovine atria, indicating a major role of the B1-adrenoceptors. Clenbuterol was only a partial agonist in rat right atria, increasing heart rate at high concentrations through stimulation of B1-adrenoceptors. In studies in vivo, clenbuterol decreased the plasma potassium concentration and increased the plasma glucose concentration. Clenbuterol also reduced diastolic blood pressure and increased heart rate. The increase in heart rate was not due to direct stimulation of cardiac B1-adrenoceptors by clenbuterol but was consistent with a reflex response to B2-adrenoceptor-mediated hypotension. This would have caused the activation of baroreceptors, which in turn would have resulted in both the release of norepinephrine to stimulate cardiac B1-adrenoceptors and the inhibition of cholinergic input to the heart. Clenbuterol may allow the full repartitioning effects seen with the B2-agonist alone, but with a markedly attenuated effect on the heart.<sup>d</sup>

### **Reviewer 2 Conclusion**

These concerns should be addressed by clear guidelines for uses that restrict applications in ‘organic animal production’.

### **Reviewer 2 Recommendation Advised to the NOSB**

Epinephrine should not be allowed in organic animal production systems. The therapeutic use of this product in organic livestock production can not be allowed in order to satisfy requirements for ‘organic animal’ production.

### References

<sup>a</sup> (Greenspan, F.S. and D.G. Gardner. 2001. Basic & Clinical Endocrinology, Lange Medical Books/McGraw-Hill, New York, NY)

<sup>b</sup>H. Huang, C. Gazzola, G. G. Pegg, and M. N. Sillence. Differential effects of dexamethasone and clenbuterol on rat growth and on  $\beta_2$ -adrenoceptors in lung and skeletal muscle. *J. Anim. Sci.* 2000. 78:604-608.

<sup>c</sup>G.S.G. Spencer and M. H. Oliver. Suppression of Immune Response in Lambs During Treatment with the Beta-Adrenergic Agonist Clenbuterol. *J. Anim. Sci.* 1996. 74:151–153.

<sup>d</sup>A. J. Hoey, M. L. Matthews, T. W. Badran, G. G. Pegg, and M. N. Sillence. Cardiovascular Effects of Clenbuterol are B2-Adrenoceptor-Mediated in Steers. *J. Anim. Sci.* 1995. 73:1754-1765

### **Reviewer 3** [Ph.D. Chemistry, Professor, Department of Chemistry, Southwest US]

#### **Summary**

Epinephrine is not synthetic; rather it is a naturally-produced hormone. It is used to treat allergic reactions, various lung diseases and glaucoma. In the first two applications, use of epinephrine can be life-saving.

There is little doubt that epinephrine is a worthwhile medication. It does have some counter-indications for use, although few of these are likely to be encountered under conditions of organic farming.

As is pointed out in the TAP report, the most significant toxic issues are related to samples that are past or near expiration dates, so this is not a flaw in the substance itself.

However, in the end, the ban on hormone use would appear to be the overriding factor.

**Reviewer 3 Conclusion**

Thus, use of epinephrine should not be allowed until the ruling on hormone use is rescinded or modified.

**Reviewer 3 Recommendation Advised to the NOSB**

At such a time as the legislation on hormone use in organic production is changed, I would suggest allowing the use of epinephrine without restrictions.

**TAP Conclusion**

All three TAP reviewers found epinephrine to be a synthetic material. One reviewer supports allowance of the substance in livestock with restrictions, while the other two recommended that epinephrine could not be allowed until the ban of hormone use in organic production is changed. These two reviewers felt that the therapeutic use of this product in organic livestock production can not be allowed in order to satisfy current requirements for 'organic animal' production. Concerns about proper dosage and product expiration were raised.