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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 573

[Docket No. 94F-0283]

**Food Additives Permitted in the Feed and Drinking Water of Animals; Menadione Nicotinamide Bisulfite**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule; republication and opportunity to file objections or additional information.

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**SUMMARY:** The Food and Drug Administration (FDA) is republishing, with additional information, a final rule that published in the **Federal Register** of January 2, 1996 (61 FR 5). The rule amended the food additive regulations (animal use) to reflect approval of a food additive petition (FAP) filed by Vanetta (U.S.A.) Inc. Objections to the final rule were filed. FDA is not acting on the objections in this document, but is clarifying the basis of approval of the petition and providing additional information. The agency also is providing a new 30-day period for the submission of objections or of additional information in support of the objections that were previously filed. FDA has not stayed the effective date of the final rule, effective January 2, 1996.

**DATES:** Objections, additional information in support of the previously filed objections, or additional written objections and requests for a hearing, must be submitted by (*insert date 30 days after date of publication in the Federal Register*).

**ADDRESSES:** Submit written objections and/or additional information in support of objections previously submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Sharon A. Benz, Center for Veterinary Medicine (HFV-228), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-6656.

**SUPPLEMENTARY INFORMATION:****I. Background**

In the **Federal Register** of January 2, 1996, FDA published a final rule that amended the food additive regulations (animal use) to reflect approval of an FAP (FAP 2228) filed by Vanetta (U.S.A.) Inc., 1770 East Market St., York, PA 17402. The final rule provides for the safe use of menadione nicotinamide bisulfite (MNB) as a nutritional supplement in chicken and turkey feeds for the prevention of vitamin K deficiency and as a source of supplemental niacin when used at a rate not to exceed 2 grams per ton (g/t) of complete feed. Heterochemical Corp., 111 East Hawthorne Ave., Valley Stream, NY 11580, filed objections to the final rule in its entirety alleging that the studies upon which the petition relies failed to conform to good laboratory practices (GLP's) or good clinical practices (GCP's), and that the regulation promotes deception of the consumer and misbranding of the product. Heterochemical's objections are:

1. The record of the studies fails to establish that any of the nonclinical laboratory studies (including target animal safety) on which the regulation is based were conducted in accordance with GLP's as described in part 58 (21 CFR part 58). The record also fails to provide, alternatively, a reason for noncompliance as required by § 571.1(k) (21 CFR 571.1(k)). Furthermore, the record does not provide a basis for identifying the differences between the practices used and those required by the GLP regulations, so as to permit an evaluation of the studies' integrity and reliability (i.e., if the target animal safety studies are flawed, there is no information in support of the safety of the food additive) (Ref. 1).

2. The record of the studies fails to establish that any of the clinical studies on which the regulation is based were conducted in accordance with GCP's as illustrated in FDA's Center for Veterinary Medicine's (CVM's) guidance document entitled "Guideline on the Conduct of Clinical Investigations: Responsibility of Clinical Investigators and Monitors for Investigational New Animal Drug Studies," October 1992 (the guidelines cited by the objection were supplanted by a revised document in May 1997) (Ref. 2).

3. Heterochemical objects to the regulation in that it establishes MNB as a source of supplemental niacin and authorizes labeling the product as a source of supplemental niacin. Based on a low level of niacin supplementation, the firm contends that the labeling promotes deception of the consumer and results in misbranding of food within the meaning of the Federal Food, Drug, and Cosmetic Act (the act).

The preamble of the January 2, 1996, final rule stated that FDA evaluated the data presented in the petition and concluded that use of the product is safe. The final rule stated that the food additive regulations would be amended as requested in the FAP. FDA is now republishing the final rule to clarify its basis for approval, and to provide additional information supporting approval of the petitioned use, specifically the GLP statement as described in § 571.1(k). FDA believes this course of action is appropriate to supplement the record. FDA will also clarify the reasons for approving the FAP, and provide Heterochemical and any other interested party with an opportunity to proffer facts that demonstrate FDA's basis for approving FAP 2228 was incorrect.

FDA is therefore republishing the final rule and providing an additional 30 days for submission of objections or of additional information in support of the objections that have already been filed. In accordance with its discretion under section 409(f) of the act (21 U.S.C. 348(f)), FDA is not staying the final rule. FDA will consider a stay, however, if one is requested, after having evaluated any objections or other information filed in response to this document.

## **II. Administrative Record**

### *A. Question of Adherence to GLP's (Part 58 and § 571.1(k))*

In filing an FAP, the petitioner is required to provide data and information to support the safe use of the product as required by section 409(c)(1) of the act. The supporting data and information include full reports of investigations made with respect to the safety of use of the additive, including information as to the methods and controls used in conducting the investigations. Part 58 prescribes GLP's for conducting those nonclinical laboratory studies that are used to support

or are intended for use to support FAP's or marketing permits for products regulated by FDA. Compliance with GLP's is intended to ensure the quality and integrity of the safety data filed to support approval of an FAP. If nonclinical laboratory studies are involved, an FAP shall include, for each study, a statement that the study was conducted in compliance with GLP requirements set forth under part 58, or if the study was not conducted in compliance with the GLP's, a brief statement with the reason for noncompliance.

In FAP 2228, Vanetta submitted a journal article (Ref. 1) supporting approval of its petition. The studies reported in the article were not conducted in accordance with GLP's, and Vanetta did not submit a statement of the reason for noncompliance. Accordingly, FDA is reopening the administrative record to include a statement from Vanetta on the reasons for the studies' noncompliance with GLP's, as required under § 571.1(k).

#### *B. Clarification of the Record*

The objections Heterochemical filed in response to FDA's approval of MNB point out that the basis for the agency's decision was not clear. The administrative record for FAP 2228 included various agency comments on the studies reported in the journal article by Oduho et al. The objector interpreted the comments to mean that the studies were invalid and thus did not support approval of the FAP. Contrary to the objector's interpretation, the agency's comments on the Oduho studies did not question their validity, and do not invalidate the agency's final decision that MNB is safe and achieves its intended technical effect. However, the objections made it clear that the agency needed to make additional comments to clarify the record.

##### 1. Target Animal Safety

FAP 2228 included the Oduho article to support safety of MNB. The Oduho article included what was described as a chronic study (Ref. 1). The results reported in the article indicated that MNB is a safe and effective source of vitamin K and niacin activities. Niacin can serve as a generic name for all pyridine-3-carboxylic acids that exhibit nicotinamide activity (Ref. 3). Only when doses exceed 1,000 times the chick's vitamin K requirement did the article's authors report

morbidity or mortality. The data generated by the chronic study, where up to 6 g of menadione per kilogram (kg) complete feed were fed to chick's, support the safety of the substance.

Although this chronic study was of relatively short duration (14 days), the agency believes that it is sufficient to support its conclusion that MNB is safe. The agency evaluated the results of the study in conjunction with the following and other available information that further supported its final determination that MNB is safe and achieves its intended technical effect. MNB hydrolyzes into menadione and nicotinamide. Menadione is prior sanctioned as a source of vitamin K activity (Ref. 4), and nicotinamide (niacinamide) is generally recognized as safe as a nutrient and/or dietary supplement under 21 CFR 582.5535 and section 201(s) of the act (21 U.S.C. 321(s)). Both components have a long history of safe use in animal diets (Refs. 4 and 5).

## 2. Utility

Menadione and many of its derivatives have vitamin K activity. This vitamin has several biological functions, one of the most important being in blood clot formation (Ref. 6). The Oduho article included a study demonstrating that inclusion of MNB in chick diets improved blood clotting when compared to negative controls. The improvements observed in the study were similar to those seen when another accepted source of vitamin K activity was added to experimental diets.

The highest level of menadione utilized in this study, 0.4 milligram (mg)/kg diet, approaches that recommended by the National Research Council, 0.5 mg/kg, for the type of birds used in this experiment (Ref. 7). The adequacy of 0.4 mg to meet the birds' nutritional requirement is demonstrated by the fact that the prothrombin times of 17 and 19 seconds for MNB and menadione dimethylpyrimidinol bisulfite (MPB), an accepted source of vitamin K activity (21 CFR 573.620), fall very close to the normal range for chickens, which has been reported to vary from 20 to 25 seconds (Ref. 8). The Oduho article reported the normal prothrombin range for chicks to be 12 to 25 seconds. The bioavailability of the vitamin K activity, supplied by the menadione component of MNB, did not differ significantly from that of the positive control substance, MPB. Both MNB and MPB were bioequivalent as an active source of menadione.

The agency noted that the levels of nicotinamide utilized in Oduho experiment number 2 are below those accepted as nutritionally adequate. However, this study did demonstrate that the nicotinamide portion of the MNB molecule was available to the chicks, i.e., that it is bioavailable to a similar extent as pure nicotinamide, which served as a control in the study. In addition, the low level of nicotinamide supplementation is closer to the level of this vitamin supplied by MNB with the mandated 2 g per ton complete feed restriction. Both the amount of nicotinamide supplied by MNB and other dietary sources of this compound will be utilized to formulate a diet which meets the animal's niacin nutritional requirements.

Vanetta amended its petition and submitted a preliminary report on clinical studies conducted at the University of Georgia. This report supported the utility of MNB as a source of vitamin K activity. Because the bioavailabilities of both the menadione and nicotinamide components of MNB were established by the Oduho article, and the utility of MNB as a source of vitamin K activity was confirmed in the University of Georgia experiments, the utility portion of the amended petition was acceptable.

### 3. Conditions of Use and Directions for Use

The approved conditions of use, as specified in the MNB regulation (21 CFR 573.625(b)), state that MNB can be used as a "nutritional supplement in chicken and turkey feeds for both the prevention of vitamin K deficiency and as a source of supplemental niacin."

The conditions of use appropriately compare the levels of vitamin K activity from menadione and nicotinamide by stating that MNB can prevent a vitamin K deficiency, but is simply a source of niacin. As noted previously, niacin can serve as a generic name for all pyridine-3-carboxylic acids that exhibit nicotinamide activity (Ref. 3). By using the different terms, the conditions of use establish that MNB provides different levels of vitamin K and niacin activities.

The directions for use on the product label specify the minimum amount of menadione and niacin in MNB, and do so in units commonly used in the feed industry (Ref. 9). Animal nutritionists routinely mix feed ingredients to obtain a complete, balanced animal diet, and the composition

of this diet normally changes with an animal's weight and age (Ref. 7). Therefore, users of the product will refer to the minimum amounts specified on the MNB label and mix feed accordingly with MNB and other sources of niacin to provide all nutritional needs based on the weight and age of the animals being fed.

Finally, the agency notes that the MNB label follows the Association of American Feed Control Officials (AAFCO) format, which the agency concluded was acceptable. AAFCO, primarily composed of State regulatory officials, has developed a set of model regulations concerning feed labeling. FDA generally concurs with the AAFCO model regulations although these model regulations are not binding. Feed manufacturers routinely follow the model regulations when labeling feed and are familiar with the AAFCO requirements.

### **III. Opportunity for Objection**

A food additive shall, with respect to any particular use or intended use of such additive, be deemed to be unsafe, unless it and its use or intended use conform to the terms of an exemption that is in effect for investigational use, or there is in effect, and it and its use or intended use are in conformity with, a regulation issued under section 409(a) of the act. With respect to any intended use of a food additive, a person may file a petition with the appropriate center within FDA proposing the issuance of a regulation prescribing the conditions under which said additive may be safely used. The petition shall, in addition to any explanatory or supporting data, contain the name of the food additive, its chemical name and composition, a statement of the conditions of the proposed use of such additive, together with all directions, recommendations, and suggestions proposed for the use of such additive with specimens of proposed labeling. The petition shall also contain relevant data bearing on the physical or other technical effect the additive is intended to produce, the quantity of the additive required to produce the desired effect, a description of practicable methods for determining the quantity of the additive in or on food and any substance formed in or on food because of its use, and full reports of investigations made with respect to

the safety of the use of the additive, including information as to the methods and controls used in conducting the investigations.

Any party who will be adversely affected by this regulation may at any time on or before *(insert date 30 days after date of publication in the **Federal Register**)*, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

#### **IV. References**

1. Oduho, G. W., T. K. Chung, and D. H. Baker, "Menadione nicotinamide bisulfite is a bioactive source of vitamin K and niacin activity for chicks," *Journal of Nutrition*, 123: 737-743, 1993.
2. "Guideline on the Conduct of Clinical Investigations: Responsibility of Clinical Investigators and Monitors for Investigational New Animal Drug Studies" ("Guideline No. 39," U.S. Department of Health and Human Services, FDA, CVM, October 1992) (superseded by "Guidance for Industry No. 58," May 1997).
3. National Research Council, *Vitamin Tolerance of Animals*, National Academy Press, 1987.
4. "Food Additive Status of Vitamin K Active Substances in Animal Food" (48 FR 16748, April 19, 1983).

5. Title 21 CFR 121.101, "Substances that are generally recognized as safe," 1974 (21 CFR part 582, 1998).

6. Suttie, J. W., "Vitamin K," *Handbook of Vitamins*, edited by L. J. Machlin, Marcel Dekker, Inc., 1991.

7. National Research Council, *The Nutritional Requirements of Poultry*, National Academy Press, 1994.

8. Swenson, M. J. "Physiological properties and cellular and chemical constituents of blood," *Duke's Physiology of Domestic Animals*, edited by M. J. Swenson, Cornell University Press, 1977.

9. *Official Publication*, Association of American Feed Control Officials, Inc., 1998.

### List of Subjects in 21 CFR Part 573

Animal feeds, Food additives.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA is republishing in its entirety the text of the final regulation that appeared in the **Federal Register** of January 2, 1998. This republication of the final rule does not amend the regulation in any way.

## **PART 573—FOOD ADDITIVES PERMITTED IN FEED AND DRINKING WATER OF ANIMALS**

1. The authority citation for 21 CFR part 573 continues to read as follows:

**Authority:** 21 U.S.C. 321, 342, 348.

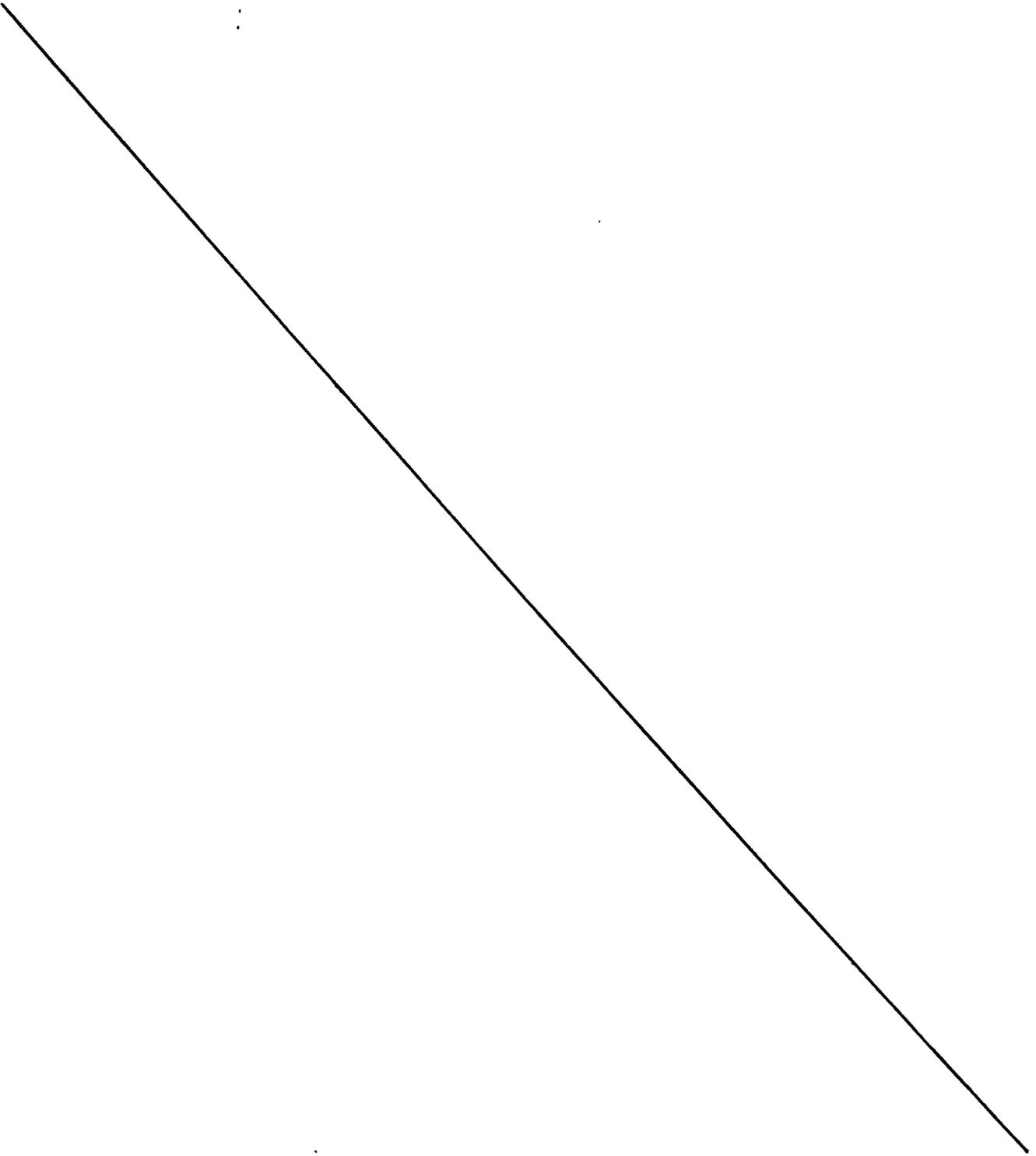
2. Section 573.625 is republished as follows:

### **§ 573.625 Menadione nicotinamide bisulfite.**

The food additive may be safely used as follows:

(a) *Product.* The additive is 1,2,3,4-tetrahydro-2-methyl-1, 4-dioxo-2-naphthalene sulfonic acid with 3-pyridine carboxylic acid amine (CAS No. 73581-79-0).

(b) *Conditions of use.* As a nutritional supplement in chicken and turkey feeds for both the prevention of vitamin K deficiency and as a source of supplemental niacin.



(c) *Limitations.* Not to exceed 2 grams per ton of complete feed. To assure safe use, the label and labeling shall bear adequate directions for use.

Dated: 8/11/99  
August 11, 1999



Stephen F. Sundlof  
Director  
Center for Veterinary Medicine

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