Boehringer Ingelheim

BOEHRINGER INGELHEIM ANIMAL HEALTH, INC.

July 16, 1998

Andrew Beaulieu, D.V.M.
Acting Director
Office of New Animal Drug Evaluation, HFV-100
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

MF 3577
BACITRACIN METHYLENE DISALICYLATE
TYPE A MEDICATED ARTICLE
GENERAL CORRESPONDENCE
MEMORANDUM OF JULY 2, 1998 TELEPHONE CONFERENCE

Dear Dr. Beaulieu:

This correspondence summarizes the items discussed on July 2, 1998 between you, [ ] and the undersigned pertaining to the subject MF for Bacitracin Methylene Disalicylate Type A Medicated Article.

The subject MF 3577 is the official document associated with the interim marketing provisions of Boehringer Ingelheim Vetmedica, Inc.'s bacitracin methylene disalicylate product as listed in 21 CFR 558.15 (the current listing of Fermenta Animal Health, Inc. does not reflect current ownership).

As we discussed at the July 2, 1998 conference, the undersigned would prepare and submit minutes of our discussion for your written response.

The initial question pertained to any new changes regarding the interim marketing provisions of 21 CFR 558.15 that may have occurred since your letter to the undersigned dated June 13, 1996. You responded that the status of the interim marketing provisions have not changed from your letter dated June 13, 1996. However, you stated that the public health concerns for antibiotic resistance (currently under consideration by CVM, CDC and the WHO) may alter the notice-and-rulemaking procedures. That is, provided documentation supporting an Agency conclusion of a public health hazard for a specific antibiotic(s) in animal feed that would require more immediate action than notice-and-rulemaking procedures.

Marketing considerations: The manufacturers of the Active Drug Ingredient (ADI) and the Type A Medicated Article must be in compliance with cGMPs. However, no VMF/DMF or NADA submissions are required prior to the marketing of a Bacitracin Methylene Disalicylate Type A Medicated Article for sponsors listed under the provisions of 21 CFR 558.15. All participants agreed that the sponsors of the ADI and the Type A Medicated Article would be subject to inspection by the FDA at any time after introduction of a regulated product into the market place.

Likewise, there was agreement among conference participants that it would be prudent for the manufacturer of the Type A Medicated Article to have 90-day accelerated stability data collected prior to marketing the

Type A Medicated Article. That is, the manufacturer of the Type A Medicated Article would be a new (alternate) manufacturing site for the Type A Medicated Article. The requirement for 90-day accelerated stability data is consistent with CVM guidance for alternate manufacturing sites of approved Type A Medicated Articles.

You offered that the changes in the manufacturing site for the 21 CFR 558.15 products are not unusual considering the length of time that has elapsed under the interim marketing provisions of 21 CFR 558.15. In addition, you stated that CVM has permitted changes in formulation, including the concentration of the active drug ingredient, for the Type A Medicated Articles covered by the interim marketing provisions.

As previously suggested in your letter dated June 13, 1996, you stated that a sponsor of a Type A Medicated Article may want to establish an INAD as a repository of information submitted for phased review. That is, manufacturing information and other documentation necessary to vacate the interim marketing by approval of an NADA for Bacitracin Methylene Disalicylate Type A Medicated Article would be submitted to this INAD. This information would be collected and submitted to the INAD after marketing of Bacitracin Methylene Disalicylate Type A Medicated Article has been re-initiated.

[ ] inquired about the DESI finalization of bacitracin containing animal drug products. Except for the conference participants were not readily cognizant of this FR publication pertaining to this bacitracin containing animal drug products. [ ] was kind enough to fax me a copy of the FR announcement on DESI finalization after our telephone conference. The final rule entitled "New Animal Drugs; Bacitracin Methylene Disalicylate and Bacitracin Zinc With and Without Penicillin" published on September 24, 1982 (47 FR 42100). For ready reference, a copy of the FR publication is included in this submission under ATTACHMENT 1. The specific products listed in 47 FR 42100 were the S. B. Penick & Co. and the Commercial Solvent Corp. products previously itemized in the FR publication dated July 17, 1970 (35 FR 11531), as amended on October 2, 1970 (for ready reference, a copy of these FR publications is included under ATTACHMENT 2.

The following comments were not discussed during the telephone conference but are the undersigned's comments on the DESI finalization of bacitracin containing Type A Medicated Articles and the provisions of 21 CRF 558.15:

The NAS/NRC review was limited to drugs approved prior to October 10, 1962. For ready reference, a copy of FDA's information sheets on announcement of FR publications dated July 9, 1966 and October 6, 1966 are included in this submission under ATTACHMENT 3 and 4, respectively.

The final rule (47 FR 42100) references applications for bacitracin alone or with penicillin that were approved prior to October 10, 1962. The aforementioned FR specifically references the July 17, 1970 FR, as amended, as the bacitracin containing products subject to DESI finalization. The bacitracin containing products listed in the final rule were the subject of some type of approval (probably an Antibiotic Form 5 or Form 6) prior to the 1962 date. The NADA numbers listed in the FR announcement were assigned by BVM in the 1970s. The FR announcement (47 FR 42100) is silent on bacitracin containing drug products approved/marketed after October 9, 1962.

Historically, it was possible for a certifiable antibiotic to be approved/marketed rather easily prior to the implementation of the New Animal Drug Amendments on August 1, 1969. Actually, approvals continued to be granted under Section 507-certifiable antibiotics-of the Federal Food, Drug, and Cosmetic Act [FFD&CA] for a few years after the August 1, 1969 date.

RE - 21 CFR 558.15: The FR publications (Proposed Statement of Policy, Statement of Policy, Proposed Rule and several related corrections/republications and additions such as the nitrofurans) precedent to the publication of a final rule listing products covered by the interim marketing provisions, are quite complex.

I am unable to determine a specific chronological time period in the FR publications pertaining to 21 CFR 558.15. I opine that products marketed prior to August 1, 1969 were definitely covered by the interim marketing provisions of 21 CFR 558.15. However, the aforementioned FR publications pertaining to 21 CFR 558.15 products may support a prior to 1973 marketing date for products listed in 21 CFR 558.15. In any event, either date provides a time period for initiating the marketing of bacitracin containing products after October 9, 1962 and finalization of the interim marketing provisions.

In my opinion, the items presented in the previous paragraphs stand mute based upon the Commissioner's conclusion in the final rule dated February 25, 1976 (41 FR 8281). Specifically, the undersigned refers to item 6 (page 8285) and item 17 (page 8287) in support of the interim marketing status of the subject bacitracin methylene disalicylate product. For ready reference, a copy of 41 FR 8281 is included in this submission under ATTACHMENT 5. Further, it is opined that a specific Agency proposal, such as notice-and-rulemaking, would be necessary to conclude the provisions of 21 CFR 558.15.

One item that we did not discuss on July 2, 1998 was the labeling claims (indications for use) for the interim marketed Bacitracin Methylene Disalicylate Type A Medicated Article. Specifically, what are the current labeling claims for the interim marketed Bacitracin Methylene Disalicylate Type A Medicated Article: (1) claims prior to DESI finalization, (2) claims reflecting DESI finalization or (3) claims currently codified in 21 CFR 558.76 and 21 CFR 510.515?

Section 21 CFR 558.15(b)(1) provides for drug levels and indications for use as itemized in 21 CFR 558.76 for chickens, turkeys, swine and cattle. However, Section 21 CFR 510.515(b)(1) does not cite 21 CFR 510.515. Historically, the product claims/use levels under 21 CFR 510.515 were approved under Section 507 (certifiable antibiotics) and Section 409 (food additives) of the FFD&CA. Data submitted under Sections 507 and 409 of the FFD&CA were not proprietary.

We anticipate and look forward to your response. If I may be of assistance, call me at (913) 380-3025.

Sincerely,

Donald A. Gable

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