C-25 **Boehringer Ingelheim**

BOEHRINGER INGELHEIM ANIMAL HEALTH, INC.

September 18, 1998

FNR'ED BY DCU ON

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Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine (HFV-1)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

MF 3577
NOPTRACIN® MD-50
BACITRACIN METHYLENE DISALICYLATE
TYPE A MEDICATED ARTICLES
GENERAL CORRESPONDENCE
RE: 21 CFR 558.15

Dear Dr. Sundlof:

We refer to your letter dated July 29, 1998 pertaining to the 21 CFR 558.15 listing of Boehringer Ingelheim Vetmedica, Inc.'s (BIVI) product, bacitracin methylene disalicylate Type A medicated article. For ready reference, a copy of your letter is included in this submission under TAB 1. The [ ] listing for [ ] Type A medicated article cited in your letter will be addressed in separate correspondence.

Initially as a representative of Fermenta Animal Health Co. (FAHC) and currently representing BIVI, I have been corresponding with CVM personnel on our MF 3577 for bacitracin methylene disalicylate for the past three years. A rather comprehensive history of the subject MF relative to the listing of our Type A medicated article in 21 CFR 558.15 was submitted to CVM on June 22, 1995. For ready reference, a copy of the transmittal letter for the June 22, 1995 submission is enclosed under TAB 2. Additional items relevant to our returning to the market place with a Type A medicated article containing bacitracin methylene disalicylate were addressed in our submissions dated March 22, 1996 and April 9, 1996. For ready reference a copy of the transmittal letter from these submissions is enclosed under TABS 3 and 4, respectively. CVM responded to all three of the aforementioned submissions by letter dated June 13, 1996. For ready reference, a copy of CVM's letter is enclosed under TAB 5.

We are continuing this ongoing correspondence with CVM on MF 3577 for bacitracin methylene disalicylate Type A medicated article. With an additional animal drug sponsor we have jointly discussed the subject MF with CVM as indicated in our submission dated July 16, 1998. For ready reference, a copy of the transmittal letter for this submission is included under TAB 6. BIVI's July 16, 1998 submission is still pending in CVM.

NOPTRACIN® MD-50 ANTIBIOTIC FEED SUPPLEMENT was a medicated premix containing bacitracin methylene disalicylate for which marketing was initiated by NOPCO (NOPCO CHEMICAL COMPANY) in the 1960s or possibly even at an earlier date. NOPCO (later, DIAMOND SHAMROCK CHEMICAL COMPANY) marketed several animal drug products containing certifiable antibiotics under

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the NOPSTRESS™ (personal knowledge and example under TAB 8). These animal drug products containing certifiable antibiotic were probably the subject of Antibiotic Form 6s as provided by section 507 of the Federal Food, Drug, and Cosmetic Act during this time period (see * NOTE). At some time point in the 1960's NOPCO became NOPCO FEED SUPPLEMENTS DEPARTMENT, BIOCHEMICALS DIVISION, DIAMOND SHAMROCK CHEMICAL COMPANY. Since that time there has been several additional ownership changes including new geographic locations, involving the records for animal drug products introduced by NOPCO. The list of previous owners / sponsors of the subject bacitracin containing Type A medicated article include NOPCO, DIAMOND SHAMROCK CHEMICAL COMPANY, SDS Biotech Corporation, Fermenta Animal Health Co. and Boehringer Ingelheim Animal Health, Inc. For clarification of the subsequent statements in this letter, our existing files (including those of Fermenta Animal Health Co.) do not contain any correspondence by a representative of NOPCO when it was an independent company.

> * NOTE: We must state that FDA's approval of an Antibiotic Form 6 could consist of applying a stamped statement (which was signed on behalf of the Commissioner) to the sponsor's transmittal letter as exemplified by the letter under TAB 7. Also, please note that the approval of the Antibiotic Form 6s continued to occur for a period of time after the enactment date for P. L. 90-399.

However, having said all of the above, the administrative record supports a conclusion that NOPTRACIN® MD-50 ANTIBIOTIC FEED SUPPLEMENT, a medicated premix containing bacitracin methylene disalicylate, is covered by the marketing provisions of section 108 of the Animal Drug Amendments of 1968, P. L. 90-399.

As part of the administrative record for NOPTRACIN® MD-50 ANTIBIOTIC FEED SUPPLEMENT, a medicated premix containing bacitracin methylene disalicylate, we present the following items:

(I). TAB 8: A label for NOPTRACIN® MD-50 ANTIBIOTIC FEED SUPPLEMENT dated 2/69 (February, 1969). Please note that this date is prior to enactment of the New Animal Drug amendments and that NOPCO had become a subdivision of DIAMOND SHAMROCK CHEMICAL COMPANY prior to February, 1969.

(II). DIAMOND SHAMROCK CHEMICAL COMPANY continued to market a medicated premix containing bacitracin methylene disalicylate during the 1970s. DIAMOND SHAMROCK CHEMICAL COMPANY and other manufacturers of bacitracin containing premixes, under the auspices of the Animal Health Institute (AHI), sponsored the studies required by 21 CFR 558.15 (previously 21 CFR 135.109). These sponsors were identified by AHI as the "Bacitracin Subgroup of the Antibacterials Research Criteria Task Force." AHI submitted MF 3596 on behalf of the sponsors participating in the aforementioned Subgroup. In support of a conclusion that both CVM and AHI members recognized DIAMOND SHAMROCK CHEMICAL COMPANY as a sponsor of an approved bacitracin containing premix, we present copies of the following correspondence under TAB 9:

(a). Letter from CVM (Dr. Guest) to DIAMOND SHAMROCK CHEMICAL COMPANY dated March 14, 1974 – MF 3577.

(b). Letter from CVM (Dr. Guest) to DIAMOND SHAMROCK CHEMICAL COMPANY dated April 1, 1974 – MF 3577.

(c). Letter from DIAMOND SHAMROCK CHEMICAL COMPANY (Dr. McKenna) to CVM (Dr. Guest) dated June 26, 1974.

(d). Letter from DIAMOND SHAMROCK CHEMICAL COMPANY (Dr. McKenna) to CVM (Dr. Guest) dated August 8, 1974 pertaining to *in vitro* studies sponsored by the aforementioned AHI "Subgroup" of sponsors for bacitracin containing premixes.

(e). Letter from DIAMOND SHAMROCK CHEMICAL COMPANY (Dr. McKenna) to CVM (Dr. Guest) dated February 26, 1976.

(f). Memorandum from AHI (Dr. Brunton) to Bacitracin Subgroup of the Antibacterials Research Criteria Task Force dated October 7, 1976. Attached to Dr. Brunton's memorandum was a letter from CVM (Dr. Guest) to AHI (Dr. Brunton) dated September 27, 1976. Please note that CVM's letter references both MF 3577 held by DIAMOND SHAMROCK CHEMICAL COMPANY and MF 3596 held by AHI on behalf of manufacturers / sponsors of 21 CFR 558.15 studies pertaining to bacitracin containing premixes.

The previous list of correspondence indicates that both the CVM and sponsors / manufacturers of competitive bacitracin products recognized DIAMOND SHAMROCK CHEMICAL COMPANY as an approved sponsor / manufacturer of a bacitracin containing premix. It is not plausible that the DIAMOND SHAMROCK CHEMICAL COMPANY would have contributed monies to the AHI coordinated studies conducted under MF 3596 if the DIAMOND SHAMROCK CHEMICAL COMPANY did not market bacitracin containing premixes.

(III). The DIAMOND SHAMROCK CHEMICAL COMPANY was omitted from the Proposed Rules listing of sponsors for bacitracin containing premixes in the FEDERAL REGISTER dated August 6, 1974 (39 FR 28382). A copy of DIAMOND SHAMROCK CHEMICAL COMPANY's (Dr. McKenna) letter to the Hearing Clerk (FDA) dated September 18, 1974 pertaining to this FEDERAL REGISTER omission is enclosed in this submission under TAB 10.

(IV). Please refer to the copy of the FEDERAL REGISTER dated February 25, 1976 (41 FR 8282) under TAB 11. The Commissioner, (1) in response to the aforementioned DIAMOND SHAMROCK CHEMICAL COMPANY submission to the Hearing Clerk (FDA) and (2) with the waiver of a failure by DIAMOND SHAMROCK CHEMICAL COMPANY to make certain technical filings by the appropriate date, concludes that DIAMOND SHAMROCK CHEMICAL COMPANY has completed the necessary filings. The Commissioner adds DIAMOND SHAMROCK CHEMICAL COMPANY to the list of sponsors of bacitracin methylene disalicylate in 21 CFR 558.15(g)(1). The undersigned opines that the basis for the conclusion of the Commissioner included a comprehensive assessment of the actions and communications by and between both the sponsor (DIAMOND SHAMROCK CHEMICAL COMPANY) and FDA / CVM personnel on the subject bacitracin methylene disalicylate premix (including MF 3577 and MF 3596).

We acknowledge the breadth of the Commissioner's assessment and have no intent to minimize the stated basis for the Commissioner's conclusion in the aforementioned 1976 FEDERAL REGISTER. However, we opine that the Commissioner's conclusion is very concise. Therefore, the additional items cited above under I and II are very relevant to documenting that NOPCO / DIAMOND SHAMROCK CHEMICAL COMPANY were marketing NOPTRACIN® MD-50 ANTIBIOTIC FEED SUPPLEMENT, a medicated premix containing bacitracin methylene disalicylate. The administrative record documents that the

DIAMOND SHAMROCK CHEMICAL COMPANY marketed a bacitracin containing premix prior to implementation of the New Animal Drug Amendments of 1968 and participated / interacted with CVM and AHI personnel as a sponsor of a bacitracin containing premix throughout the 1970s. Likewise, throughout the 1970s, DIAMOND SHAMROCK CHEMICAL COMPANY was recognized as an approved sponsor / manufacturer by CVM personnel and by AHI members. The AHI members of the aforementioned AHI "Subgroup" included manufacturers of competitive bacitracin containing products.

In addition, the administrative record demonstrates that DIAMOND SHAMROCK CHEMICAL COMPANY took responsibility as a sponsor to support the investigative studies to continue to be in compliance with the regulatory requirements of 21 CFR 558.15 for bacitracin containing premixes (please refer to the previously cited MF 3596 and MF 3577). The actions of the DIAMOND SHAMROCK CHEMICAL COMPANY were consistent with ownership / sponsorship of a legitimate approval of a bacitracin containing premix.

While I can not offer certification, it is the knowledgeable opinion of the undersigned that FDA probably approved one or more Antibiotic Form 6s for NOPCO's bacitracin containing premixes. However, this opinion appears to be a mute issue based upon certification specifications in your letter enclosed under TAB 1.

That is, and in accordance with your July 29, 1998 letter, the undersigned can certify the Food and Drug Administration accepted DIAMOND SHAMROCK CHEMICAL COMPANY's Master File 3577 for premixes containing bacitracin methylene disalicylate prior to February 25, 1976. The CVM receipt date for MF 3577 is February 25, 1974. In addition, the undersigned certifies that DIAMOND SHAMROCK CHEMICAL COMPANY participated / financially supported through sponsorship the 21 CFR 558.15 studies, coordinated by AHI under MF 3596, so that DIAMOND SHAMROCK CHEMICAL COMPANY could continue to market their bacitracin containing premixes. Likewise, the undersigned can certify that the label for the NOPCO FEED SUPPLEMENT DEPARTMENT, DIAMOND SHAMROCK CHEMICAL COMPANY premix containing bacitracin methylene disalicylate is consistent with 21 CFR 558.15 (please refer to the copy of labeling enclosed under TAB 7).

As requested by your letter dated July 29, 1998, the undersigned includes the following statement in this letter: "I certify that all the statements made in this letter are true and complete to the best of my knowledge and ability and that the attached new animal drug label is a true and complete copy. I understand that, as with any other statements provided to the Food and Drug Administration, willfully making a false certification is a criminal offense under U.S. Code, Title 18, Sec. 1001."

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

Sincerely,

Donald A. Gable

Donald A. Gable, D.V.M.
Manager, Pharmaceutical Regulatory Affairs
Boehringer Ingelheim Vetmedica, Inc.

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