FERMENTA ANIMAL HEALTH

CONFIDENTIAL

AIRBORNE EXPRESS

MF 3577 - NOPTRACIN® MD-50
BACITRACIN METHYLENE DISALICYLATE
TYPE A MEDICATED ARTICLE

June 22, 1995

Richard E. Geyer
Deputy Director
Office of Surveillance and Compliance (HFV-200)
Center for Veterinary Medicine

and

Dianne T. McRae, DVM
Generic Animal Drug and Quality Control Staff (HFV-102)
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Dear Mr. Geyer and Dr. McRae:

MF 3577: NOPTRACIN®-40 (ZINC BACITRACIN)
AND NOPTRACIN® MD-50 (BACITRACIN METHYLENE DISALICYLATE)

TAB 1 - Bureau of Veterinary Medicine's letter dated March 14, 1974 on protocols for bacitracin studies.

TAB 2 - Diamond Shamrock Chemical Company's transmittal letter dated June 26, 1974 with submission of protocols for bacitracin studies.

TAB 3 - Diamond Shamrock Chemical Company's transmittal letter dated August 8, 1974 with submission of *in vitro* studies on bacitracin.

TAB 4 - Diamond Shamrock Chemical Company's letter dated September 18, 1974 to the Hearing Clerk pertaining to sponsorship of zinc bacitracin and bacitracin methylene disalicylate, i.e., omission from the Federal Register Notice of August 6, 1974 (39 FR 28382).

TAB 5 - Please refer to Federal Register dated February 25, 1976 (41 FR 8282). Specifically, we make reference to item 17 on page 8287 of the February 25, 1976 Federal Register.

Comments: The Diamond Shamrock Chemical Company's letter dated September 18, 1974 (TAB 4) requests listing as an approved sponsor of zinc bacitracin and bacitracin methylene disalicylate. The Federal Register of February 25, 1976 (41 FR 8287) (TAB 5) is incorrect in stating that the Diamond Shamrock Chemical Company questioned its omission from the list of sponsors in § 558.15(b)(2). Diamond Shamrock Chemical Company's letter makes no mention of zinc bacitracin and bacitracin methylene disalicylate in combination with other animal drug products.

Fermenta Animal Health Company, P.O. Box 338, 15th & Oak, Elwood, KS 66024 • 913/365-9070

CONFIDENTIAL

The Federal Register is correct in listing the Diamond Shamrock Chemical Company as an approved sponsor of bacitracin methylene disalicylate under § 558.15(b)(1) as the Diamond Shamrock Chemical Company was manufacturing premixes containing 50 g/lb bacitracin methylene disalicylate (NOPTRACIN® MD-50). That is, item 17 on page 41 FR 8287 states that: ".....Diamond Shamrock has now completed the necessary filings and the Commissioner has added Diamond Shamrock to the list of sponsors of antibacterial premixes for bacitracin methylene disalicylate in § 558.15(g)(1)." The critical element identified in the Federal Register was the participation in the 21 CFR 558.15 safety studies, not the existence of an approved Form 4 or Form 6 for Diamond Shamrock Chemical Company's bacitracin MD (NOPTRACIN® MD-50).

The omission of NOPTRACIN® 40 from the Federal Register of February 25, 1976 remains an unknown. As we are not planning on manufacturing and marketing a ZINC BACITRACIN TYPE A MEDICATED ARTICLE at this time, we have no immediate concerns regarding this omission from the February 25, 1976 Federal Register.

TAB 6 - Diamond Shamrock Chemical Company's transmittal letter dated February 26, 1976 with submission of *in vivo* studies on bacitracin.

TAB 7 - Animal Health Institute's memorandum dated October 7, 1976 with attached Bureau of Veterinary Medicine letter dated September 27, 1976.

Comments: The Bureau concludes that the bacitracin data satisfies the criteria for safety as specified by the Antibiotics in Animal Feeds Task Force. The September 27, 1976 letter from the Bureau for Veterinary Medicine to the Animal Health Institute identifies two (2) Master Files for bacitracin, MF 3577 and MF 3596. Perhaps, at the initial implementation of activity associated with the present 21 CFR 558.15, there were separate MF for bacitracin MD and zinc bacitracin.

TAB 8 - Please refer to the Federal Register dated March 11, 1977 (42 FR 13548). This Federal Register changes the listing in 21 CFR 558.15(g)(1)&(2) from the Diamond Shamrock Chemical Company to Diamond Shamrock Corp.

TAB 9 - The present listing in 21 CFR 558.15(g)(1) is for Fermenta Animal Health Co. Please refer to Federal Register dated August 8, 1986 (51 FR 28546). The Diamond Shamrock Corp. had it name changed to SDS Biotech Corp. prior to becoming Fermenta Animal Health Co.

TAB 10A - Diamond Shamrock Chemical Company's letter dated November 10, 1975 pertaining to [redacted] NOPTRACIN®-40 and NOPTRACIN® MD-50 sent to Mr. Robinson, Chief, Certification Services Branch, Bureau of Drugs.

TAB 10B - Diamond Shamrock Chemical Company's letter dated December 9, 1975 pertaining to [redacted] NOPTRACIN®-40 and NOPTRACIN® MD-50 sent to Dr. Guest, Bureau of Veterinary Medicine.

CONFIDENTIAL

TAB 10C - Diamond Shamrock Chemical Company's letter dated December 19, 1975 pertaining to NOPTRACIN®-40 and NOPTRACIN® MD-50 sent to Dr. Guest, Bureau of Veterinary Medicine.

TAB 11 - Bureau of Veterinary Medicine's letter dated March 8. 1976 responding to Diamond Shamrock Chemical Company's letters dated November 10, 1975 (TAB 10A) and December 19, 1975 (TAB 10C) pertaining to NOPTRACIN® 40 and NOPTRACIN® MD-50.

Comments: The Bureau's letter is silent on the December 9, 1975 letter, TAB 10B (in 1975, the position held by Dr. Guest at the time had no responsibilities for For ready reference, copies of the labels for

NOPTRACIN® MD-50 are also included under TAB 11.

There were no objections in the Bureau of Veterinary Medicine's letter dated March 8. 1976 to the marketing NOPTRACIN®-40 and NOPTRACIN® MD-50 premixes. The objections were to the marketing of

Conversely, the Bureau of Veterinary Medicine and the Food and Drug Administration responded to the Diamond Shamrock Chemical Company's letter dated September 18, 1974 to the Hearing Clerk pertaining to sponsorship of zinc bacitracin and bacitracin methylene disalicylate (TAB 4) by listing Diamond Shamrock Chemical Company in the Federal Register dated February 25, 1976 (41 FR 8282, TAB - 5, page 8287). The Bureau of Veterinary Medicine and the Food and Drug Administration (the Commissioner) concluded that adequate documentation of approval of Diamond Shamrock Chemical Company's NOPTRACIN®-40 and NOPTRACIN® MD-50 premixes existed to satisfy the transitional provisions (Section 108) of Public Law 90-399, Animal Drug Amendments of 1968. Items 6 and 7 (page 8285) specifically addressing the basis for listing sponsor in 21 CFR 558.15(g)(1)&(2). We quote from item 6:

> "The Commissioner has thoroughly reviewed the files on all drugs and sponsors or which commitments were received to conduct the studies required by this regulation, and the only drugs and sponsors which the Commissioner has determined to be approved for use by NADA, NDA, master file, antibiotic regulation or food additive regulation have been listed." (Emphasis added.)

The Commissioner concludes all drugs and sponsors listed in 21 CFR 558.15(g)(1) were approved for use by NADA, NDA, master file, antibiotic regulation or food additive regulation (as we discuss later, the only exception is

CONFIDENTIAL

In the mid-1960s, a backlog of medicated feed applications existed in the Division of Veterinary Medicine in the Bureau of Drugs and after November 7, 1965 the Bureau of Veterinary Medicine. This review time for medicated feed applications exceeded one year. Sponsors started adding certifiable antibiotics to combination animal drug products so that they could get a quick approval from the Division of Antibiotics and Insulin Certification, Bureau of Science (became Certification Services Branch, Bureau of Drugs). This resulted in a rather extensive 21 CFR 144.26 which provided for 1 or more certifiable antibiotic and/or 1 nitrofuran and/or 1 organic arsenical and/or 1 coccidiostat. Remnants of 21 CFR 144.26 currently remain codified under 510.515 (40 FR 13802, March 27, 1975). Medicated feeds containing a certifiable antibiotic, regardless of the number of active drug ingredients, were approved by a Form 10 submission rather than a FORM FDA 1800 (now FORM FDA 1900).

Again, please refer to Federal Register dated February 25, 1976 (TAB 5 - 41 FR 8282). Specifically, we make reference to pages 8285-8288 of the February 25, 1976 Federal Register. The following list itemizes examples of certifiable antibiotics in combination animal drug products (some with bacitracin MD) which met contemporary BVM/FDA standards:

Item 7 - certifiable antibiotic & antihistomonad

This combination of carbarsome and bacitracin methylene disalicylate is important as the Commissioner concludes that "the NADA for Whitmoyer's combination product was approved under contemporary efficacy requirements." If the combination drug product meets contemporary efficacy requirements, it is concluded that each of the active ingredients meet contemporary efficacy requirements.

Item 9 - certifiable antibiotics & coccidiostat

The conclusion is the same as item 7, except that the combination is buquinolate and bacitracin methylene disalicylate or zinc bacitracin.

Item 16 - certifiable antibiotics & coccidiostat & organic arsenical

The conclusion is the same as item 7, except that the combination is clopidal, roxarsone and bacitracin methylene disalicylate or zinc bacitracin.

Item 19 - certifiable antibiotic & coccidiostats & potentiated coccidiostat & organic arsenical

Item 20 - certifiable antibiotics & coccidiostat

Item 23 - certifiable antibiotics & coccidiostats & potentiated coccidiostat & organic arsenical

Items 19, 20 and 23 are simply annotated as they exemplify that a significant number of combination animal drug products containing a certifiable antibiotic(s) were approved under contemporary efficacy criteria.

It should be noted that except for manufacturing methods, facilities and controls, data submitted under Section 507 of the Food, Drug, and Cosmetic Act, as Amended,

CONFIDENTIAL

for certifiable antibiotics have had no proprietary rights. Some of the Diamond Shamrock Chemical Company's letters are misleading as to the significance of the authorization letters from [redacted]. Likewise, item 17 in the February 25, 1976 Federal Register (page 8287) is also misleading as to the representation of these authorization letters. No distinction is recognized as to the differences in the proprietary nature of Section 505 data vs. the nonproprietary nature of Section 507 data in either the February 25, 1976 Federal Register or in Diamond Shamrock Chemical Company's letters. That is, all that was needed for a Form 4 or Form 6 approval of a certifiable antibiotic that was the subject of an previously approved Form 5 were a label and a batch formulation. Further, item 17 in the February 25, 1976 Federal Register incorrectly states "letters from the holders of NADA's for bacitracin methylene disalicylate" when one letter was for bacitracin methylene disalicylate and a second letter was for zinc bacitracin.

TAB 12 - As with the Federal Register of February 25, 1976 under TAB 5, The Federal Register dated April 8, 1977 (42 FR 18611) includes additional combinations with bacitracin methylene disalicylate. Specifically, we refer to the following:

> Item 4a - amprolium & ethopabate & bacitracin methylene disalicylate or zinc bacitracin & roxarsone
>
> Item 5 - zoalene & bacitracin methylene disalicylate or zinc bacitracin & arsanilic acid
>
> Item 7a - amprolium & bacitracin methylene disalicylate or zinc bacitracin & penicillin
>
> Item 7g - nicarbazine & bacitracin MD & roxarsone

The comments made above in the discussion of the combination animal drug products listed in the February 25, 1976 Federal Register apply equally to the combination drug products listed in the Federal Register dated April 8, 1977.

In addition, please refer to the copy of the April 20, 1973 Federal Register (38 FR 9811) under TAB 12. Specifically, we refer to the beginning of § 135.109 on page 9813:

> "§ 135.109 Antibiotic and sulfonamide drugs in the feed of animals.
>
> (a) The Commission of Food and Drugs will propose to revoke currently approved subtherapeutic ( increased rate of weight gain, disease prevention, etc.) uses in animal feed of antibiotics and sulfonamide drugs whether granted by approval of new animal drug application, master files and/or antibiotic or food additive regulation, by no later than 2 years following the effective date of order unless data are submitted which resolve conclusively the issues concerning their safety to man and animals and their effectiveness under specific criteria established by the Food and Drug Administration based on the guidelines in the report of the Task Force on the use of antibiotics in animal feeds."

The Statement of Policy and Interpretation in the April 20, 1973 Federal Register

CONFIDENTIAL

resulted in requests from sponsor for the withdrawal of several hundred approved combinations of animal drug products for use in animal feed. The combination animal drug products continued to be sponsored in 21 CFR 558.15 were the subject of some type of prior approval. The Bureau of Veterinary Medicine did not add new combination drug products as a result of the April 20, 1973 Statement of Policy and Interpretation.

We offer the following comments regarding the FDA Task Force guidelines mentioned in the April 20, 1973 Federal Register's Statement of Policy and Interpretation. Collectively, there are three (3) guidelines for Antibacterial Drugs in Animal Feeds: (1) Human Health Safety Criteria, (2) Animal Health Safety Criteria and (3) Antibacterial Effectiveness Criteria.

The Human Health Safety Criteria and Animal Health Safety Criteria have, in part, been implemented since 1973. Granted the specific studies required have evolved over time and many of the criteria are no longer requirements. Certainly, the issues associated with the safety concerns have been the subject of public discussions.

To the best of our knowledge, the Antibacterial Effectiveness Criteria have not been implemented. For prospective (single ingredient and combination) animal drug products, other BVM/CVM guidelines have adequately addressed the issue of effectiveness. Again, to the best of our knowledge, retrospective application of the Antibacterial Effectiveness Criteria to the animal drug products listed in 21 CFR 558.15 has not been initiated. To reiterate, the approvals for some of the animal drug products listed in 21 CFR 558.15 were not supported with data meeting contemporary efficacy standards.

[ ]

TAB 13 - We refer to Diamond Shamrock Chemical Company's letters dated March 15, 1971 and August 9, 1971 pertaining to [ ] sent to Certification Services Branch, Bureau of Drugs. Likewise, we refer to Certification Services Branch's, Bureau of Drugs letters dated May 28, 1971 and September 21, 1971.

Comments: Please note that this correspondence is roughly two years after the effective date (August 1, 1969) of Section 512, Public Law 90-399, Animal Drug Amendments of 1968. We mention these NADAs for the following reasons:

Even in 1971, it was extremely easy to get a Section 507 approval (Form 4 or Form 6) for a certifiable antibiotic. Also, it exemplifies the non-proprietary status of data submitted under Section 507.

TAB 14 - Please refer to Diamond Shamrock Chemical Company's letter dated June 17, 1971 and the Bureau of Veterinary Medicine letter dated June 29, 1972.

Comments: Please note the contrasting response to the June 17, 1971 submission by Diamond Shamrock Chemical Company pertaining to [ ] to Certification Services Branch, Bureau of Drugs. We refer to the Bureau of Veterinary Medicine letter dated June 29, 1972 and the correspondence previously cited under TABS 10A.

CONFIDENTIAL

10B, 10C and 11. It was not easy to get a FORM FDA 356 approval under Section 512 even in the 1970s.

Also, note that March 15, 1971 and August 9, 1971 letters pertaining to[ ] sent to Certification Services Branch, Bureau of Drugs brackets the date that the June 17, 1971 initial submission by Diamond Shamrock Chemical Company pertaining to[ ] to Certification Services Branch, Bureau of Drugs, which was forwarded to the Bureau of Veterinary Medicine for review.

Finally, we opine that [ ] and [ ] are discussed solely for illustration of specific preclearance and regulatory requirements in BVM/FDA, i.e., the NADAs are for [ ] not premixes.

TAB 15 - We were still manufacturing BACITRACIN MD-50 as discussed in Interoffice Correspondence dated May 19, 1978.

Concluding Comments: Alternatively, having said all of this, we did not need to stop marketing bacitracin MD premixes. We could have continued to market bacitracin MD premixes as the following companies have continued to market the itemized premixes: (1) Pennfield Oil Co. - oxytetracycline premixes & chlortetracycline premixes & oxytetracycline-neomycin premixes, (2) SmithKline Beecham Animal Health (now Pfizer, Inc. - chlortetracycline premixes and (3) Pfizer Inc. - oxytetracycline-neomycin premixes. The combination oxytetracycline-neomycin premixes (a premix with a fixed formulation) have never been approved for use by NADA, NDA, master file, antibiotic regulation or food additive regulation.

We respectfully submit that we could legally initiate production tomorrow, validate the first 3 production batches and return to the market place with a BACITRACIN METHYLENE DISALICYLATE TYPE A MEDICATED ARTICLE, e.g., FERMENTRACIN® MD-50. We anxiously await your review and comments

Thanks again for your continued and thoughtful cooperation.

Donald A. Gable

Donald A. Gable, DVM
Director, Special Projects
Regulatory Affairs

Desk Copies:
Dr. Donald L. Campbell, HFV-102
Mr. Richard E. Geyer, HFV-200
Ms. Patsy W. Gardner, HFV-246
Dr. Dianne T. McRae, HFV-102

dag:648