

Buchanan Ingersoll
ATTORNEYS

Edward John Allera
(202) 452-7985
alleraej@bipc.com

1776 K Street, N.W.
Suite 800
Washington, DC 20006-2365

T 202 452 7900
F 202 452 7989
www.buchananingersoll.com

September 8, 2003

VIA HAND DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2003N-0324: Request for Hearing Regarding NADA 138-939
(Pennfield Oil Co.)

To Whom it May Concern:

As counsel for Pennfield Oil Company/Pennfield Animal Health ("Pennfield"), we are requesting a hearing under 21 CFR § 12.21 ("Initiation of a hearing involving the issuance, amendment, or revocation of an order") and the Notice of Opportunity for Hearing ("NOOH") published in the Federal Register ("FR") of Friday, August 8, 2003.¹ According to the NOOH, the Agency apparently believes that the only claims that can be made for a neomycin ("neo")/oxytetracycline ("oxy") product such as Pennfield's NEO-OXY (marketed under NADA 138-939) are those Drug Efficacy Study Implementation ("DESI") claims that were found to be effective in a 1:1 ratio. However, as we will illustrate below, the bases for FDA's contentions that the Agency's previous findings of effectiveness for all of the claims, indications, species and combinations of the NEO-OXY that are approved and codified in 21 CFR § 558.15(g)(2) have been undermined, have not been set forth in the notice. Nor have the bases for CVM to assert that new adequate and well-controlled studies are necessary for these claims and species been set forth. These facts are particularly relevant due to the long history of the approved uses of these drug products and the bases for FDA's prior conclusion. In this request for hearing, we outline our rationale why a hearing is necessary to resolve questions for claims and for ratios for NEO-OXY listed in § 558.15(g)(2).² In order to resolve the numerous issues that surround the approval status of NADA 138-939, an administrative hearing is required. In accord with the NOOH, Pennfield will provide facts and evidence to demonstrate that genuine and substantial issues of material facts are in dispute that require a formal evidentiary hearing for resolution.

2003N-03240

¹ 68 FR 47332 (August 8, 2003).

² 68 FR 47332, 47335-47336 (August 8, 2003).

HERA

I. INTRODUCTION

A. DESI Review of Neomycin and Oxytetracycline

The 1962 Kefauver-Harris Drug Amendments ("1962 Amendments"),³ effective October 10, 1962, were significant to new drug approvals⁴ in that, for the first time, FDA required drug sponsors to not only demonstrate safety of the new drug (which had been the only requirement prior to this time), but also effectiveness. The 1962 Amendments also applied retroactively, so that drugs already approved for safety were required to go through an additional review process to establish their effectiveness. The review was conducted by the National Academy of Sciences ("NAS") and the National Research Council ("NRC"), and was known popularly as the DESI program.

The 1968 Animal Drug Amendments ("1968 Amendments"),⁵ which added § 512 to the Federal Food, Drug, and Cosmetic Act ("FFDCA"), simply codified all of the then-existing animal drug statutory provisions. Prior to this time, animal drugs were approved in four different ways: (1) new drugs, (2) master files, (3) antibiotics, and (4) food additives.⁶ Section 507, which was added to the Act in 1945,⁷ required FDA to certify batches of drugs composed in whole or in part of penicillin, without regard for whether the use was in humans or other animals.⁸ This section operated much as a monograph and general rule, with the findings applicable to all identical, related, and similar drugs.⁹

As part of the DESI review process, both neomycin sulfate¹⁰ and oxytetracycline¹¹ were evaluated by the NAS/NRC. The review found neomycin sulfate to be *probably effective* for use in control and treatment of bacterial enteritis in cattle, horses, sheep, goats, swine, dogs, cats, turkeys, chickens, ducks, and mink, and as a wet antibacterial dressing in

³ PL 87-781, October 10, 1962.

⁴ At this time, the new drug provisions applied to humans as well as other species.

⁵ PL 90-399. (July 13, 1969).

⁶ See § 108(b)(2) of the 1968 Amendments, PL 90-399.

⁷ 68 FR 47272, 47272 (August 8, 2003), citing P.L. 79-139.

⁸ 68 FR 47272, 47272-47273 (August 8, 2003). This section was later amended to include, in addition to penicillin, streptomycin, chlortetracycline, bacitracin, chloramphenicol, and derivatives of these antibiotics. *Id.* at 47273.

⁹ Section 507 was repealed by the Food and Drug Administration Modernization Act (FDAMA) of 1997. See PL 105-115, November 21, 1997. Identical, related, or similar drugs are discussed in 21 CFR § 310.6 ("Applicability of "new drug" or safety or effectiveness findings in drug efficacy study implementation notices and notices of opportunity for hearing to identical, related, and similar drug products") for human drugs; the definition of an identical, related, or similar drug product as stated in § 310.6 is cross-referenced in 21 CFR § 514.235 ("Judicial review") for animal drugs. "Identical, related, or similar" drugs are also mentioned in § 558.15 ("Antibiotic, nitrofurans, and sulfonamide drugs in the feed of animals"). There is no identical counterpart to the human drug regulation § 310.6 in the animal drug regulations.

¹⁰ 36 FR 837 (January 19, 1971).

¹¹ 35 FR 7089 (May 5, 1970).

swine, cattle, sheep, and dogs. FDA concurred with these findings.¹² During the review of oxytetracycline, NAS/NRC found the drug to be (1) *effective* for use in treatment of hexamitiasis, and (2) *probably effective* for control and treatment of specific diseases of livestock and poultry, and that use may result in faster gains and improved feed efficiency under appropriate conditions.¹³ The Agency concurred in this evaluation for oxytetracycline, and made two additional conclusions as well.¹⁴ As the NOOH indicates, the NAS/NRC review process only addressed the single-ingredient feed use products; NAS/NRC did not conduct a review of efficacy data related to combinations of these drugs. Nevertheless, FDA did review certain NEO-OXY combinations, and the Agency approved them. These approvals are codified, in part, in § 558.15(g)(2).

B. Promulgation of "Interim" Marketing Regulation, 21 CFR § 558.15

In its final rule amending § 558.15, FDA stated that "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."¹⁵

In the most recent version of § 558.15,¹⁶ the so-called "interim marketing" provision, Pennfield is listed as a sponsor for oxytetracycline for the species, use levels, and indications for use as listed in § 558.450 ("Oxytetracycline"). Further, Pennfield is listed in § 558.15(g)(2) as a sponsor for a neomycin/oxytetracycline combination drug for chickens, turkeys, swine, and calves at a variety of use level combinations and many indications for use. It is this listing in (g)(2) which is most important since, according to that subsection, the combinations listed in (g)(2) are permitted when made from articles listed in (g)(1):

The following is a list of drug combinations permitted when prepared from antibacterial Type A articles listed in paragraph (g)(1) of this section. Drug

¹² 36 FR 837 (January 19, 1971).

¹³ 35 FR 7089 (May 5, 1970). Note that for oxytetracycline, all three products evaluated were manufactured by one company. The soluble powder that was evaluated was deemed "effective" and "probably effective" for the indications listed above. The other two products, both premixes, were evaluated solely as "probably effective" for the same indications listed above in (2). This notice defined, in one instance, "livestock" to include swine, cattle, sheep, rabbits, and mink, and "poultry" to include broiler chickens, laying chickens, and turkeys.

¹⁴ 35 FR 7089 (May 5, 1970). Specifically, FDA stated: "1. The claims for hexamitiasis should be included under the susceptible host. 2. Appropriate claims regarding faster weight gains and improved feed efficiency should be stated as 'For increased rate of weight gain and improved feed efficiency for (under appropriate conditions of use).'" *Id.*

¹⁵ 41 FR 8282, 8285 (February 25, 1976). See also July 29, 1998 letter from Stephen Sundlof to Dr. Donald Gable, attached as exhibit D to complaint, Alpharma, Inc. v. McClellan, Case #8:03-cv-01406-PJM, May 13, 2003.

¹⁶ April 1, 2003.

combinations listed in subpart B of this part name their sponsors and are incorporated herein by reference since they are safe and effective by contemporary standards, ...¹⁷

Therefore, as explained above, Pennfield has lawful approval for all of the claims/indications/species listed in § 558.15(g)(2). As discussed in the request for hearing for its bacitracin methylene disalicylate animal drug products, which discussion is incorporated herein by reference, FDA has substantive rulemaking authority. The Agency used that authority specifically to provide a public record of the approvals for the combination antibacterial animal drug products. Those approvals are listed in § 558.15(g). Those approvals are the legal equivalent of New Animal Drug Applications ("NADA's") approved under § 512 of the FFDCA, and are entitled to all of the legal and due process protections accorded NADA's. The use levels listed in § 558.15(g)(2) vary from species to species and indication to indication, often reflecting a range of concentrations of both neo and oxy that can be used.¹⁸ FDA's proposed action seeks to withdraw approval of all these various strengths, species and combinations other than the new claims and species in the 1:1 ration. To accomplish this legal condition precedent, FDA must therefore meet all of the applicable legal, scientific, and due process requirements. Genuine and substantial issues of material fact are in dispute about the Center's proposed action that require a hearing for resolution. We will discuss these facts further below in the context of the Agency's claims that only 1:1 ratios can be made.

II. CURRENT NEO-OXY CONTROVERSY

A. FDA's Administrative Posture

In its August 8, 2003 NOOH, FDA appears to have taken the position that the Agency believes Pennfield only has lawful approval for the 1:1 DESI-reviewed claims listed in Tables 2-5.¹⁹ The language immediately preceding those tables is ambiguous at best, however, and at worst (for FDA) actually tends to suggest that there is no negative finding of effectiveness for claims made in other than 1:1 ratios:

FDA has determined that its previous findings of effectiveness for the single ingredients are applicable to the combinations *in the absence of information indicating interference in effectiveness between individual ingredients*. The Agency's review also considered information about the effectiveness submitted to these two

¹⁷ 21 CFR § 558.15(g)(2) (2003).

¹⁸ For example, in the listing for "chickens (first 2 weeks)," the use levels are 50-100 g/ton oxy and 35-140 g/ton neo base. Based on these ranges, it is conceivable that many different ratios, including fractional ratios, of the two components in a neo/oxy combination could be used. See § 558.15(g)(2).

¹⁹ 68 FR 47332, 47335-47336 (August 8, 2003).

NADAs, although this information did not alter the Agency's conclusions based on the single-ingredient findings (emphasis added).²⁰

In addition to the lack of clarity and precision of the NOOH with respect to NADA 138-939, Pennfield also takes issue with the Agency's complete failure to cite to any new evidence showing that neo and oxy in anything other than a 1:1 combination is ineffective. We take up these issues in greater detail below.

B. Legal Framework

The multiple ratios and species of neomycin and oxytetracycline approvals are codified in §558.15 (g)(2). FDA has recognized these approvals through the rulemaking process.²¹

The rule was promulgated in 1976, twelve years after the Drug Amendments of 1962 imposed the requirement for proof of effectiveness by adequate and well-controlled studies for drugs approved initially before 1962. The Agency interpreted this statutory requirement as adding a requirement that each component in a combination make a contribution to the effect. As noted, FDA contracted with the NAS/NRC to review the data submitted on the drugs marketed under previously approved and all identical, similar or related drug products, the Drug Efficacy Study Implementation Review (DESI Review).

In the rule FDA then states that all the approvals listed in § 558.15(g)(2) meet the contemporary criteria and standards for showing that they are safe and effective for the indications, conditions, species and use levels set forth. The standard at that time was adequate and well-controlled studies in accord with § 514.117. Extensive combinations of neomycin and oxytetracycline in multiple ratios for all the major animal species were listed and thus found to be effective.

Since the findings and rule confirmed the legal approvals for the drug products listed, Congress has twice amended the FFDCA to reduce the data required to show that an animal drug product is effective, in order to reduce unnecessary duplicative research. The Generic Animal Drug and Patent Term Restoration Act of 1988 (GADPTRA) was enacted, in part, to facilitate generic animal drug approvals through Abbreviated New Animal Drug Applications (ANDA's). But it served other functions. One was to encourage new product development. A second was to clarify and simplify the legal and scientific basis for approval of older animal drug products under the rubric of hybrid NADA's, § 512 (n)(5), which are the animal

²⁰ 68 FR 47332, 47334 (August 8, 2003).

²¹ FDA's recognition of all approved § 558.15(g)(2) provides further undisputed evidence that it considers the rulemaking procedure a binding rule of law rule that provides public acknowledgment of these approvals. As such, this recognition calls into question the Agency's entire procedure and arguments concerning Pennfield's bacitracin approvals in the companion discussion elsewhere in the NOOH.

drug equivalent to § 505(b)(2) applications in the human drug area. These provisions and the CVM policy letters illustrate that CVM has historically considered a wide variety of data, information, expertise, expert opinion, treatises, literature, and label revisions in concluding that drugs subject to the DESI review were effective. Further, the amalgamation of information was applied widely to all identical, similar and related animal drug products.

The Animal Drug Availability Act of 1996 further eases the legal and scientific requirement for showing effectiveness by eliminating the requirement for 2 adequate and well-controlled studies to show effectiveness. Only one such study is now required along with other appropriate evidence. (§ 512(d)(3))

In summary, CVM concluded that all of the combinations, strengths, and species of neomycin and oxytetracycline set forth in § 558.15(g)(2) were supported by substantial evidence of effectiveness, *i.e.* the contemporary legal and scientific standard. The Center reached these conclusions after consideration of the data submitted under the DESI review, the literature, independent expert review, the Center's expertise, and other relevant scientific factors and considerations. Further, Congress has eased the standards that are applicable to establish the effectiveness of the combinations. The facts surrounding these issues are material to resolution of this matter, and Pennfield will provide evidence to support them.

C. FDA has Failed to Meet its Burden of Coming Forward with Adequate Evidence to Undermine the NEO-OXY Approval

The NOOH in cavalier, general terms asserts a complete reversal of FDA's position on these drug products. It is a position followed by the industry and the Agency for almost 30 years. The NOOH also ignores two statutory amendments to ease the requirements for proof of effectiveness. With no public data, analysis, or rationale for changing its previous conclusions about the effectiveness of the neomycin-oxytetracycline combinations, CVM asserts neomycin and oxytetracycline only in a ratio of 1:1 have been shown to be effective for the claims set forth in Tables 2-5 in the NOOH. These claims cover all major species: poultry (chicken and turkey), swine, sheep and cattle. The Center also now states that neomycin and oxytetracycline are effective as individual components from a vast range of 10 - 500 milligrams/ ton and 10-50 mg/ lb. The standard for establishment of contribution of effectiveness is evidence of noninterference between the two components. The Center therefore proposes to withdraw approval of all other claims and indications in the NADA's as codified in § 558.15(g)(2).

CVM has failed to meet its initial legal burden as set forth most clearly in Hess & Clark. It has failed to provide specific factual notice about the basis for undermining its previous conclusions that the drug products listed in § 558.15(g)(2) are effective. That requirement exists where the standard the Agency seeks to apply is derived from a specific

notice or regulation. The requirement is particularly relevant in the instant case because the approvals that CVM is proposing to revoke cover the same multiple species, and the strengths that are acceptable in the ratio of 1:1. The Center's finding of effectiveness for the 1:1 ratio is based on the DESI findings and its review of that data.

As stated above and will be shown by evidence, these conclusions have historically been based on data from a wide variety of numerous sources, *e.g.* expert opinion, literature, literature reviews, Agency expertise, studies of various animal species, *in vitro* studies.

CVM's attempt to assert that new, adequate and well-controlled studies are necessary to establish the effectiveness of all the approved claims and ratios that it is proposing to withdraw is also subject to material factual dispute. The quality and quantity of data that the Agency has used to reach its conclusion about NEO-OXY in a 1:1 ratio have been used previously under the rubric of adequate and well-controlled studies for the claims for which the Agency is now seeking to withdraw approval. Of equal importance is the absence of any data supporting the Center's position that the data extant undermine the previous determinations of effectiveness for the approved neo/oxy combinations and claims. CVM cannot merely make this assertion. It must provide the basis for that conclusion to the affected parties to analyze and rebut its applicability.

CVM must further show how the data that permit the conclusion that neo/oxy is effective in a 1:1 ratio but at levels indicating that range by a multiple of 50 in multiple species undermine the conclusion that the combination lacks effectiveness in different ratios within the vast ranges permitted.

CVM has found that neo/oxy is effective in all the major species within this vast range. It must further show that the data somehow are not extrapolatable among species and not useful in showing that the combinations are effective in different ratios.

It appears that the recent litigation over bacitracin methylene disalicylate ("BMD") initiated by Alpharma, Inc. ("Alpharma")²² served as the catalyst for FDA's actions in issuing the NOOH and proposed rule to remove certain regulations. This might be evidenced by the fact that the portion of the NOOH relative to Pennfield's NADA 141-137 for Pennitracin MD 50-G is, relatively speaking, more detailed than the portion of the NOOH relative to Pennfield's NADA 138-939 for NEO-OXY. We suspect that, since the Agency took the position in the litigation that it needed to clarify matters with respect to BMD,²³ FDA decided to cobble together - in a single NOOH - the other combination drugs from § 558.15 that had not been codified elsewhere in part 558, subpart B. As a result, FDA did not take the time to properly come forward with the evidence needed to show why Pennfield cannot make the

²² Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003.

²³ Motion for Enlargement of Time, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, July 10, 2003, at ¶ 3.

claims it is currently making for NEO-OXY. According to the Act, the Secretary must have new information suggesting that a drug is not efficacious for all of the claims it is making.²⁴ FDA states in the NOOH that the "new information" that constitutes its coming forward now is "that provided by the NAS/NRC reviews."²⁵ It is unclear how the DESI reviews, which were conducted decades ago, can now be considered "new information." As a result, we believe that FDA has not appropriately set forth in the NOOH on what "new information" the Agency is basing its actions.

D. Pennfield will provide information showing that genuine and substantial issues of material fact exist that require a hearing for resolution.

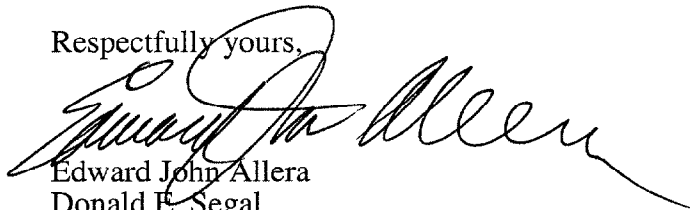
In addition to the foregoing, Pennfield will provide the following:

1. Adequate and well controlled studies, equivalent to the data showing that neo-oxy is effective at a ratio of 1:1 for the claims set out in Tables 2-5 in the NOOH, to show that neo-oxy is effective at a ratio of 2:1 for those claims.
2. Substantial evidence to support the claims for neo-oxy set forth in § 558.15(g)(2).

III. CONCLUSION

For the reasons set forth, Pennfield respectfully requests a hearing on the foregoing issues to provide evidence and will provide the remaining required evidence to support its position on these matters by October 7, 2003 as required in the NOOH.

Respectfully yours,



Edward John Allera
Donald E. Segal
Todd A. Harrison
Barbara A. Binzak
Buchanan Ingersoll P.C.

Counsel to Pennfield Oil Co./
Pennfield Animal Health

²⁴ Section 512(e)(1)(C) of the Act, codified at 21 USC § 360b(e)(1)(C).

²⁵ 68 FR 47332, 47339 (August 8, 2003).