

Declaration of Donald A. Gable, DVM
In Support of Pennfield Oil Company/Pennfield Animal Health's
Request for Hearing re: NADA 138-939 (NEO-OXY)

Docket No. 2003N-0324

1. My name is Donald A. Gable. I presently reside at 4501 Stonecrest Terrace, St. Joseph, Missouri, 64506.
2. I received my Doctor of Veterinary Medicine ("DVM") degree from Ohio State University in 1960. My list of professional qualifications is attached as Exhibit 1.
3. I am currently working as an independent contractor in the position of Consultant in Pharmaceutical Regulatory Affairs, and as a sub-contractor in the position of Senior Food and Drug Administration ("FDA") Regulatory Affairs Associate with Herschel J. Gaddy & Associates in St. Joseph, Missouri. I have been retained in my independent contractor capacity by Pennfield Oil Company/Pennfield Animal Health (collectively "Pennfield") and their legal counsel, Buchanan Ingersoll P.C., to provide my expert opinion in this matter because of my expertise in FDA/Center for Veterinary Medicine ("CVM") animal drug regulatory matters, including the history of the new animal drug approval ("NADA") process.
4. I have been employed as both a Consultant and Senior FDA Regulatory Affairs Associate since 2000. As an independent contractor working as a Consultant, I provide consulting services and compliance strategies for the preparation, compilation, and filing of, as well as follow-up on, various human and animal drug submission documents. I also provide consultation and preparation services for animal testing protocols for studies, and I provide assistance on understanding the animal drug regulations, as well as FDA/CVM policies and procedures.
5. Prior to my work as a Consultant, I was employed at Boehringer Ingelheim Vetmedica, Inc. ("BIV") from 1996 to 2000 as Manager of Pharmaceutical Regulatory Affairs. In this position, I was responsible for managing the registration of animal drug products, including new chemical entities, for approval and marketing worldwide. I also was involved in the global registration of products that had been previously manufactured by my former employer, Fermenta Animal Health Company ("Fermenta"). In December 1995 Fermenta was sold to BIV.
6. Prior to my employment at BIV, I was employed at Fermenta from 1991 to 1996 as the Director of Special Projects in Regulatory Affairs. While at Fermenta, I was involved in the preparation of NADAs for submission to FDA and the preparation of applications for submission to regulatory authorities in foreign countries as well. I was also involved in all stages of animal drug safety and efficacy studies. Finally, I provided expertise in the regulation of animal drugs in the United States and Canada and evaluated regulation requirements in other countries as well.
7. Prior to my employment at Fermenta, I was employed at CVM within FDA from 1965 to 1991 in numerous capacities, including most recently (1983-1991) as the Director of the Division of Therapeutic Drugs for Food Animals. Of particular relevance to this

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declaration is the fact that I was employed as a Staff Officer in the Office of the Center Director from 1968-1971, where I was intimately involved in the organization and execution of the Drug Efficacy Study Implementation ("DESI") review process.

8. Prior to serving in the Office of the Center Director at CVM from 1996-1968, I was responsible for organizing the The National Academy of Sciences/National Research Council ("NAS/NRC") review process, including deciding upon the twelve categories of active drug ingredients to be reviewed, which together comprised more than 700 NADAs and certifiable antibiotic submissions then on the market. These products were on the market on the grounds that they were covered by an NADA, a new drug application ("NDA"), a master file, an antibiotic regulation, or a food additive regulation, or they were exempt from regulation on grounds that they were generally recognized as safe ("GRAS"). It was not until the enactment of the Animal Drug Amendments of 1968 ("1968 Amendments") that § 512 was added to the Federal Food, Drug, and Cosmetic Act ("FFDCA"), which codified approvals for animal drugs that had been granted by the above-listed mechanisms and which provided for the modern-day NADA approval process.
9. The NAS/NRC review process was initiated as a direct result of the passage of the 1962 Kefauver-Harris Drug Amendments ("1962 Amendments"). Whereas prior to passage of the 1962 Amendments only safety data was required for human and animal drugs, after the passage of these Amendments both safety and efficacy data were required to be presented. The DESI review process was intended to provide efficacy reviews of active drug ingredients for drug products already on the market, but which prior to their marketing had been evaluated for safety only. The National Academy of Sciences/National Research Council ("NAS/NRC") aided FDA in the conduct of this efficacy review process, beginning in 1966. The NAS/NRC/DESI review process was a review process of broad claims and species, and those claims and species, and indications for use have subsequently been refined.
10. Before the NAS/NRC review process, CVM requested information from manufacturers of drug products already on the market, as well as other interested parties. In addition, scientific literature was reviewed and information from FDA's files was utilized by the expert reviewers. On the basis of this agglomeration of information, NAS/NRC made findings and subsequent recommendations to CVM based on these findings. Both NAS/NRC reviewers and FDA reviewers relied upon their own expertise during the review process, and as discussed in the NAS/NRC/CVM contract the expertise of the scientists was a primary criterion in the decision-making process.
11. FDA published the NAS/NRC's findings in the Federal Register ("FR"). I was involved in the publication process of these findings. Furthermore, I was part of a group that used the NAS/NRC/DESI review findings, along with our expertise, to determine which claims sponsors could make on their labels. Claims that were sanctioned based on the NAS/NRC findings were applied identically for every applicant whose drug product contained a given active drug ingredient. After the DESI findings were published in the FR one of the preclearance review divisions at CVM met with sponsors on the content of the labeling.

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12. Furthermore, between 1971 and 1976 I was employed as an Assistant to the Director in the Division of Nutritional Sciences, where I was responsible for evaluating NADAs relating to the production uses of drug products.
13. Intermittently I was still involved in discussions with NAS/NRC because the DESI review process was still ongoing; in fact, decades after the DESI review process began, it is still not completed. Over the past decade, I have observed CVM's actions with regard to numerous animal drug products covered by the DESI review for which no finalization and withdrawal of approval of the claims not supported by substantial evidence of effectiveness was completed. Many of these drugs and drug products utilized broad claims and species. Ultimately, narrower, more refined claims were subsumed within these broad claims.
14. As a result of my employment history and familiarity with the DESI review process, I am familiar with the requirements of the NADA approval process, and I understand that data showing a drug product is both safe and effective as these terms here evolved due to changes in the FFDCa, must be provided in an NADA. I am also familiar with the requirements for filing a supplemental NADA.
15. The DESI review findings were applied to all drug products approved under the FFDCa, as amended, as well as to all identical, related, or similar drug products containing the same active ingredients. As such, the data reviewed by NAS/NRC and CVM was considered as a whole, and included published data, data submitted by drug sponsors, revisions in labeling, Agency expertise, and the expertise of the NAS/NRC panel members. Individual pieces of data were not segregable from the whole body of data that established safety and effectiveness of the active drug ingredients and drug products.
16. According to the NAS/NRC Project of Evaluation of Veterinary Drug Efficacy and my experience, the NAS/NRC did conduct review of combination drugs during the DESI review process. The Federal Register shows that the NAS/NRC reviewed almost a dozen products of neomycin and oxytetracycline in combination. Lists of those notices are enclosed in the submission as Exhibit 2. The NAS/NRC panel members were provided with guidelines for review of data. They were informed that they would receive data from the drug companies manufacturing and marketing the drug products and labeling. They were also provided under the terms of the contract with information provided by the FDA data on which the FDA/NAS/NRC concluded that extrapolation of data and information from other species would be helpful, and according to the contract, they were informed that "in the final analysis, however, the evaluation will depend on the expertise of the individual panel members."
17. As noted in a seminal reference on CVM DESI activity, Compendium of Veterinary Drug Efficacy by Shotwell and Carr, the NAS/NRC findings are accepted by FDA to support the correctness of dosage and appropriateness of label claims for any given drug. Because the NAS/NRC evaluation is public information, its incorporation into applications for FDA premarket approval removes most normal requirements for detailed data supporting effectiveness as well as safety to the species to be treated. This procedure has resulted in significant economic savings to generic drug manufacturers and

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- has relieved FDA of the necessity of reviews of data to support registration of those drugs where were evaluated by the NAS/NRC and found effective and *probably effective*.
18. DESI review findings of less than effective were upgraded to effective based on labeling revisions, published data, expert opinion, field investigations, and previously approved indications, among other factors. This "hybrid" of data would thus support DESI upgrades of claims. This procedure was followed for decades.
 19. For certain combination drug claims the NAS/NRC did not conduct certain reviews during the DESI review process. This would include for example, neomycin/oxytetracycline combination. Rather, FDA made determinations about the effectiveness of combination drugs by basing its decisions on the DESI review process findings for the individual drug product components of the combination, its expertise, and the expertise of experts.
 20. At the time the 1962 Amendments were enacted, animal drug claims were often broad general claims for species. Once the DESI review findings (including labeling requirements) were made, such findings were applicable to all holders of legal animal drug product approvals regardless of whether granted by FFDCA, the Animal Drug Amendments of 1968, or any other way, *e.g.*, by rulemaking for sulfonamides. FDA has historically considered, as its best public policy, that congruent labeling of pioneer and generic drug products as well as of identical, related, or similar drug products should exist.
 21. CVM has reiterated this policy in its third policy letter following the passage of the Generic Animal Drug and Patent Term Restoration Act ("GADPTRA") in 1988. Under that policy a pioneer sponsor could copy a generic innovation without submission of additional data. Furthermore, according to the letter, "CVM believes that these interpretations would meet important goals of the generic legislation: to avoid duplicative research, to provide incentive for generic sponsors to innovate, and to make the conditions of use of the pioneer and generic drugs the same to the maximum extent possible." The desire to have congruent labeling has long existed, especially when multiple companies and experts generated data, and that data was evaluated with the Agency's expertise.
 22. In my capacity at CVM, I became familiar with the promulgation of 21 C.F.R. §§ 558.15 and 558.15(g). The promulgation of both 21 C.F.R. § 558.15 and § 558.15(g) involved notice-and-comment rulemaking, and the Agency considered which companies held legal approvals for various animal drug products. One key reason why rulemaking was chosen was to obtain the input of the public and to provide clear public notice about the legal status of drug products then on the market and eligible for marketing. This is one function of FFDCA § 512(i): to provide public notice of approvals.
 23. 21 C.F.R. § 558.15 was originally conceived by the Agency as an "interim" marketing regulation in an attempt to bring order to, and legitimize the marketing of, all the products marketed at that time under the 1968 Amendments and to all identical, related, or similar drug products whose sponsors filed commitments to do additional work on the drugs. CVM did this because a large number of drug products was being marketed at that

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time without Agency knowledge or regulation. However, a court ruling forced the Center to adjust its proposal, before finalization. As a result of the court case that is cited in the preamble to the final rule promulgating 21 C.F.R. § 558.15(g), the Agency allowed only those drugs that had approvals under the FFDCA to be listed in 21 C.F.R. § 558.15. The Agency had reviewed its records and data that the sponsors had supplied, and determined that the companies to be listed in 21 C.F.R. § 558.15(g) had legal new animal drug approvals. Therefore, those sponsors listed in 21 C.F.R. 558.15(g) have the equivalent of a full legal approval for their listed drug product(s).

24. I am familiar with GADPTRA and the fact that CVM issued nine policy letters following the passage of GADPTRA. I was a member of the Generic Animal Drug Committee that drafted the first eight policy letters. These policy letters were drafted in order to interpret the provisions of GADPTRA as that law would be applied by CVM.
25. Under GADPTRA, applications for generic animal drug products (abbreviated new animal drug applications, "ANADAs") are approved on the basis of findings of safety and effectiveness from "pioneer" animal drug applications, on the application of publicly available data, and on the scientific literature, among other factors.
26. GADPTRA and the nine policy letters issued by CVM are consistent with CVM's historic policies of treating antibiotics generally as a class. Like human drug products, animal drug products that were approved followed a similar broad approach to the utilization of data, including the application to all species, uses, and indications. DESI review data that applied to the upgrading of claims or finalization came from a variety of sources.
27. Through the DESI review process and subsequent enactment of GADPTRA, applications were approved in a variety of ways, including through the reliance upon safety and effectiveness data from numerous sources in order to show that drug products are effective. Such applications are now recognized as "hybrid" NADAs. One of the functions of such applications is to provide consistent, identical labeling.
28. I am familiar with the Animal Drug Availability Act of 1996 ("ADAA") and its changes to the definition of the term "substantial evidence" as it relates to proving the effectiveness of new animal drug products including products such as the neomycin-oxytetracycline combinations addressed in the NOOH. Prior to enactment of ADAA, the statutory term was defined as evidence from adequate and well-controlled investigations, including field studies. Since 1996 substantial evidence is now expanded, per 21 C.F.R. § 514.4, to include studies such as a study in the target species, a study in laboratory animals, field study, *in vitro* study, and other studies on which basis qualified experts could reasonably conclude that the drug will have the effect that it purports to have in its labeling, and the studies were performed by qualified experts, are repeatable, that the responses reliably reflect effectiveness, and that valid inferences can be drawn to the target population. For combination drugs for use in animal feed, one need only show, based on such evidence that the components make a contribution to the effectiveness for drugs containing components that are approved individually for the same use and are physically compatible.

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29. I know that Pennfield Oil Company/Pennfield Animal Health (collectively "Pennfield") owns NADA 138-939, and that the NADA covers a number of products currently marketed by Pennfield as NEO-OXY™.
30. I know that Pennfield is listed in 21 C.F.R. § 558.15(g)(2) for approval for a Type A article consisting of the combination of neo/oxy for the species, use levels, and indications for use listed therein. In addition, the use levels in 21 C.F.R. § 558.15(g)(2) for Pennfield's listing in many cases reflect a range of permitted use levels for neo and oxy for any given species/indication listed therein, indicating that a variety of ratios of neo:oxy are safe and effective. Furthermore, the language of (g)(2) states, "[d]rug 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, or such sponsors have been notified of any additional safety or efficacy data required on an individual basis."
31. In 1976, that language meant that evidence from field studies established that the drugs were effective at the ratio of 1:1 and 2:1 and in wide dose range. For neo-oxy the dosage range from 0.05-10 mg/head and from 10 gm-500 gm ton of feed in poultry, swine, sheep and cattle. The Animal Drug Availability Act of 1996 ("ANDAA") has revised and refined the standard of effectiveness as FDA has stated in the preamble in the rulemaking process to make it more flexible.
32. In the NOOH, CVM states that the 1:1 ratio of neo and oxy is effective in the dosage ranges mentioned above. There is no basis for determining how it reached a conclusion that the combination is effective at that ratio over the vast dose ranges and conditions. There is also no basis for concluding that the data and information that FDA uses to support these conclusions undermines its previous conclusion about the effectiveness of the combination in a 2:1 ratio. The Agency's decision with regard to the 2:1 combination is especially confounding, scientifically, because many approved uses for the 2:1 ratio fall within the wide dosage range acceptable for the drug in a 1:1 ratio. There is also no way to address the rationale by which CVM has undermined its previous conclusions, especially since enactment of the ADAA, without the Center providing that review and analysis of these data for analysis. That has not been done, despite a request to provide that analysis.
33. Unlike the matters involving *e.g.*, diethylstilbestrol, the nitrofurans, and other Center actions that were based on purported reevaluations of the Agency's prior decisions and the data and reanalysis were described in detail, no such thing has been done here.
34. Neomycin has been used alone and in the ratios and dose ranges cited in the NOOH for almost 50 years. Oxytetracycline has been used for a similar amount of time. The combination has been used for almost as long. In fact, it is my recollection and belief that data in CVM's files for neo-oxy combinations that were subject to the stringent review criteria applied prior to enactment of the ADAA now meet the contemporary definitions of substantial evidence of effectiveness due to the imposition of the noninterference provision. I am aware of no evidence that the combination lacks evidence of effectiveness. Requests for such information have been made of CVM, and in the absence of such information, analysis of the Agency position is impossible.

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Confidential Commercial and/or
Trade Secret Documents Redacted:

- Exhibit 1 Professional Qualifications of Donald A. Gable.
- Exhibit 2 Excerpts from: *Compendium -- Veterinary Drug Efficacy*, National Academy of Science - National Research Council, c. 1976.

Declaration of Andrew L. Winstrom
In Support of Pennfield Oil Company/Pennfield Animal Health's
Request for Hearing re: NADA 138-939 (NEO-OXY™)

Docket No. 2003N-0324

1. My name is Andrew L. Winstrom. I presently reside at 14040 Industrial Road, Omaha, Nebraska.
2. I am currently employed as the President of Pennfield Animal Health in Omaha, Nebraska.
3. I have been employed as President of Pennfield Animal Health since 1988. As President, I own Pennfield Animal Health and act as manager of Pennfield Animal Health's affairs.
4. New animal drug application ("NADA") 138-939 is owned by Pennfield Oil Company/Pennfield Animal Health (collectively "Pennfield"), and covers products that Pennfield currently markets as NEO-OXY™, which are neomycin ("neo")/oxytetracycline ("oxy") Type A combination drug products (Exhibit 1).
5. I know that Pennfield is listed in 21 C.F.R. § 558.15(g)(2) for approval for a Type A article that is made of the combination of neo/oxy for the species, use levels, and indications for use listed therein. Furthermore, many times ranges of use levels for neo and oxy are listed in 21 C.F.R. § 558.15(g)(2) for the species and indications listed therein. This demonstrates that a variety of ratios of neo:oxy are effective and necessary. In addition, 21 C.F.R. § 558.15(g)(2) states that "[d]rug 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, or such sponsors have been notified of any additional safety or efficacy data required on an individual basis." To the best of my knowledge and recollection, Pennfield has never been asked to supply any additional safety or efficacy data regarding the neo/oxy combination drug product listed in 21 C.F.R. § 558.15(g)(2).
6. I know that Mr. Gregory P. Bergt, Director of Research & Development at Pennfield Oil Company received a letter dated July 29, 1998 from Dr. Stephen F. Sundlof, Director of the Center for Veterinary Medicine ("CVM") (Exhibit 2). This letter outlined the purpose of 21 C.F.R. § 558.15, and stated that "the Agency intended to include in the 21 C.F.R. § 558.15 listings only new animal drugs or combinations of new animal drugs and conditions of use approved by one of the mechanisms described above." However, this same letter also indicated that FDA was "unable to reconstruct from its records the existence of an approval for" Pennfield's neomycin/oxytetracycline product. Therefore, the Agency asked "that such sponsors, if they have information...establishing that an approval corresponding to a specific listing in section 558.15 was granted prior to the February 25, 1976, publication date of 21 C.F.R. § 558.15, identify the involved product(s) and certify the approval status to the Agency."
7. Furthermore, I know that Mr. W.L. Winstrom, Chairman of Pennfield Oil Company, sent a letter, dated August 6, 1998 (Exhibit 3), to Dr. Sundlof in response to Dr. Sundlof's July

Declaration of Andrew L. Winstrom Re: NADA 138-939

Confidential Commercial and/or
Trade Secret Documents Redacted:

- Exhibit 1 Pennfield Animal Health Labels for NEO-OXY™ Products.
- Exhibit 2 Letter from Stephen Sundlof, CVM to Gregory P. Bergt, Pennfield Oil Co., dated Jul 29, 1998.
- Exhibit 3 Letter from W.L. Winstrom, Pennfield Oil Co. to Stephen Sundlof, CVM, dated Aug. 8, 1998.
- Exhibit 4 Letter from Stephen Sundlof, CVM to W.L. Winstrom, Pennfield Oil Co., dated Aug. 28, 1998.