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 141-137 (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] In its Notice, the Agency indicated that, with respect to New Animal Drug Application ("NADA") 141-137 for Fortracin MD 50 (BMD),[2] "[w]e are not aware of any additional approved indications beyond those listed in the original § 558.76 from 1976 for Pennfield Oil Co.'s product."[3] In this request for hearing, we outline our rationale for why a hearing is necessary to address the approval status of NADA 141-137. Numerous factors, including a lengthy administrative history of 21 CFR §§ 558.15 and 558.76, as well as a lengthy history of correspondence and filings regarding the approval of bacitracin methylene disalicylate ("BMD") itself, show that the approval status of Pennfield's NADA is complex. Nonetheless, as we will demonstrate, Pennfield has lawful approval of NADA 141-137, not only for the claims that were approved as part of the Drug Efficacy Study Implementation ("DESI") review process, but also for those claims that were subsequently approved as well. Specifically, Pennfield believes it has lawful approval for all claims as listed in § 558.76 as clarified under DESI and, of equal import, FDA's subsequent actions. Pennfield will submit facts and scientific evidence from adequate and well-controlled studies, as FDA has historically used that term, for all claims and drug products covered by the DESI review process to confirm the approval of its drug products for all these uses. In order to resolve the numerous factual and regulatory issues that surround the approval status of NADA 141-137, an administrative hearing is required. It is important to ensure that the record is complete and that all interested parties must have access to the lengthy record surrounding the approval

[1] 68 FR 47332 (August 8, 2003).
[2] Pennfield is marketing its product under NADA 141-137 as "Pennitracin MD 50-G." We believe the August 8, 2003 FR notice to be erroneous in this respect.
[3] 68 FR 47332, 47334 (August 8, 2003).

2003N-0324/B

HER 1

of NADA 141-137, particularly because of the complex nature of the issues involved, the decades of correspondence, unilateral Agency actions, and Agency litigation. As illustrated below, although we believe the Agency has not provided adequate notice and has not met its burdens of going forward, we will, in accordance with the NOOH and regulation, provide additional materials, including the data and analysis upon which this request for a hearing relies, by October 7, 2003, to the extent possible. Due process requires that the Agency provide additional information for Pennfield to address all the relevant issues.

I. INTRODUCTION

A. Summary of the Current Controversy - Procedural Background

On May 13, 2003, Alpharma, Inc. ("Alpharma"), which sells a Type A medicated article containing BMD,[4] filed a complaint in the U.S. District Court for the District of Maryland (Greenbelt) against named defendants Mark B. McClellan, Commissioner of Food and Drugs of the Food and Drug Administration ("FDA"), and FDA itself. The complaint alleged that (1) FDA unlawfully granted Pennfield approval to sell and market BMD as a new animal drug in violation of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act") and its implementing regulations or, alternatively, (2) FDA unlawfully facilitated Pennfield's false representation of FDA approval for BMD.[5] FDA filed a motion for an extension of time to file an answer, which was granted.[6]

During the extension, FDA published three documents in the Federal Register: (1) a notice of opportunity for hearing ("Certain Antibiotic New Animal Drug Products and Use Combinations Subject to Listings in the New Animal Drug Regulations; Drug Efficacy Study Implementation; Notice of Opportunity for Hearing"),[7] (2) a proposed rule ("New Animal Drugs; Removal of Obsolete and Redundant Regulations"),[8] and (3) a final rule ("New Animal Drugs for Use in Animal Feeds; Chlortetracycline, Procaine Penicillin, and Sulfamethazine").[9] While the lawsuit has since been dismissed,[10] Pennfield is requesting a hearing on NADA 141-137 for Pennitracin MD 50-G as set forth in the NOOH. We provide below our analysis of the administrative approval of NADA 141-137 for BMD, demonstrating by four nonexclusive arguments why Pennfield has lawful approval. We summarize these arguments briefly here, before providing historical information regarding BMD and the applicable regulations, and additional support for our arguments for lawful approval. As noted, these issues establish legal and factual questions. Additional materials

---

[4] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 1003, at ¶ 6.
[5] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 2.
[6] Motion for Enlargement of Time, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, July 10, 2003. Alpharma opposed FDA's motion. Opposition to Defendants' Motion for Enlargement of Time, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, July 11, 2003. FDA's motion was granted by the Court on July 11, 2003 by a paperless order.
[7] 68 FR 47332 (August 8, 2003).
[8] 68 FR 47272 (August 8, 2003).
[9] 68 FR 47237 (August 8, 2003).
[10] Stipulation and Order of Dismissal, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, August 13, 2003. This case was dismissed with prejudice.

that support our position will be submitted in accordance with the NOOH and regulation by October 7, 2003.

B. Summary of Pennfield's Arguments for Lawful NADA Approval

First, Pennfield has lawful NADA approval, by regulation, under 21 CFR § 558.15 ("Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals") for the uses and indications listed in § 558.76 ("Bacitracin methylene disalicylate"). Both Fermenta Animal Health ("Fermenta," a predecessor in interest of Pennfield)[11] and AL Labs ("AL Labs," a predecessor in interest of Alpharma)[12] are listed in 21 CFR § 558.15 as having interim marketing approval for BMD for use in chicken, turkeys, swine, and cattle for the use levels and indications for use listed in the cross-reference to 21 CFR § 558.76. While this provision was originally conceived as an "interim" provision which would eventually be withdrawn once all of the information in it was codified in part 558, subpart B, complete codification and withdrawal has never occurred. Section 558.15 still appears in the most recent version of the CFR.[13] As a result of the rulemaking procedure, those sponsors who are listed in the provision have codification of their legal equivalent of full NADA approval for the species, use levels, and indications that are referenced in the section. That was one stated purpose of the rulemaking.[14] FDA's rules are governed by plain language and reasonable interpretation and they are binding as a matter of law.[15] Therefore, Pennfield has lawful approval for the four species listed in § 558.15 (chickens, turkeys, swine, and cattle) for the uses and indications listed in § 558.76.

Two additional species, pheasants and quail, were species that were considered under the Drug Efficacy Study Implementation ("DESI") review process.[16] Those claims were upgraded to be effective as part of the DESI Review process. As such, legal claims for these species are part of the DESI Review process and thus may be made by any manufacturer until FDA withdraws their legal approvals. Therefore, Pennfield has lawful approval for its NADA for the additional species of pheasants and quail as well. Furthermore, FDA implies in the NOOH that part of the underlying reason for its actions now is that the Agency was mistaken in not appropriately updating § 558.15 over the years.[17] No mistake occurred; the approvals exist as a matter of law. Accordingly, factual scientific and other questions exist about the applicability (or inapplicability) of the existing data and facts that preclude withdrawal of the legal approval for the disputed applications without a formal evidentiary

---

[11] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 1003, at ¶ 44.
[12] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 1003, at ¶ 33.
[13] April 1, 2003. FDA now proposes to withdraw § 558.15 in its August 8, 2003 proposed rule, which will be further discussed herein. *See* 68 FR 47272 (August 8, 2003).
[14] *See e.g.*, 39 FR 28393 (August 6, 1974) (proposing addition of (g)(1) and (g)(2)) and 41 FR 8282 (February 25, 1976) (final rule).
[15] *See e.g.*, Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609 (1973) and National Nutritional Foods Ass'n v. Weinberger, 512 F.2d 688 (2d Cir. 1975).
[16] In 35 FR 11531 (July 17, 1970), FDA published its response to the DESI Review conducted by the National Academy of Sciences/National Research Council (NAS/NRC). Claims for "poultry" as a group were considered. 21 C.F.R. § 558.76(d)(1) footnotes the first two listings in the table, including certain claims for chickens, turkeys, pheasants, and quail, as those that were reviewed by NAS/NRC and found effective.
[17] 68 FR 47332, 47334 (August 8, 2003).

hearing. Additional factual questions exist about FDA's assertion that errors were made by the Agency that further require a hearing for resolution before any of the labeled conditions for use can be legally withdrawn. No assertion of "mistake" can inure to Pennfield's detriment, and cannot serve as part of the basis for FDA's current actions.

Second, sponsors of animal drugs listed in § 558.15 for which FDA had an incomplete administrative record were asked by the Center for Veterinary Medicine ("CVM") in 1998 to certify that the sponsor was entitled to be listed in that provision as having received lawful approval for the sponsor's NADA prior to February 25, 1976, the date of publication of § 558.15.[18] CVM's action was a legal redundancy because of the rule. Boehringer Ingelheim Vetmedica ("BIV"), Pennfield's immediate predecessor in interest for NADA 141-137, provided this certification to CVM.[19] In response, CVM provided BIV with a December, 1998 response letter indicating that the company could rely on FDA's December, 1998 correspondence as confirmation of the approval of NADA 141-137.[20] This letter from CVM provides Pennfield with further evidence that it has lawful approval of its NADA, and that it has the legal right to be listed in § 558.15. Factual questions exist surrounding the Center's action, including correspondence, meetings, telephone conversations, etc. A hearing is required to resolve these issues before FDA can withdraw these existing approvals

Third, Pennfield believes its lawful approval for all the claims and species is in accord with FDA's nearly half-century of procedures for implementation of the DESI Review that was reaffirmed by the 1988 Generic Animal Drug and Patent Term Restoration Act ("GADPTRA")[21], and the policy letters that CVM issued following the Act.[22] The DESI Review considered data from all public and privates sources. These data were considered as a whole and unsegregable, and served as the basis for the DESI findings and finalizations. For decades, the DESI findings have been applied not only to the drug products marketed under NADAs (or previously New Drug Applications ("NDAs")), antibiotic regulations (both certified and exempt), food additive regulations, Generally Recognized as Safe ("GRAS") determinations, and master files, but also to all identical, related, or similar animal drugs.[23] Findings of less than effective could be upgraded to effective by revisions in labeling, published data, expert opinion, field investigations, and other data. Because the foundation of the safety and effectiveness findings were a hybrid of data, the finalizations were applied to all identical, related, or similar drug products.[24] No changes in the labeling for the

---

[18] *See* July 29, 1998 letter from Stephen Sundlof to Dr. Donald Gable, Manager, Pharmaceutical Regulatory Affairs, BIV, attached as Exhibit D to Alpharma's complaint.
[19] *See* September 18, 1998 and November 17, 1998 letters from Dr. Donald Gable to Stephen Sundlof.
[20] *See* December 17, 1998 letter from Stephen Sundlof to Dr. Donald Gable.
[21] PL 100-670, November 16, 1988.
[22] These policy letters are available on CVM's website at http://www.fda.gov/cvm/index/gadaptra/gadaptra.html.
[23] *See e.g.*, 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") and 21 CFR §§ 514.235 ("Judicial review") and 558.15 (both of which mention "identical, related, or similar" drug products). There is no identical counterpart to the human drug regulation § 310.6 in the animal drug regulations.
[24] *See e.g.*, 21 CFR § 310.6, 21 CFR § 514.235, and 21 CFR § 558.15.

identical, related, or similar drug products were legally mandatory until FDA proposed to withdraw approval of the indications that were found to be less than effective due to the lack of evidence and finalized that action after a hearing or the acquiescence of the holder of the approval.[25]

In the legislative history of GADPTRA, which formalized the abbreviated new animal drug application ("ANADA") process for generic animal drugs, it was noted that a "paper NADA," *i.e.*, a hybrid, is to be treated as an ANADA.[26] "Hybrids," like paper NDAs in the human drug area, are those approvals for new animal drugs in which sponsors may rely on safety and effectiveness data from other sources to show that the two drugs are equivalent as well as obtaining additional claims.[27] CVM's seventh policy letter[28] implementing GADPTRA discusses "hybrid applications." "Hybrids" are those applications that FDA proposed in its letter to accept "for changes requiring the review of investigations conducted by or for the applicant, including changes in dosage form, strength, route of administration, and active ingredients (in a combination product), as well as new indications and new species."[29] CVM indicated in its letter that these hybrids would rely on a listed animal drug's approval, along with any data that is needed to support the change. All is necessary to comport with CVM's recognized goals of the legislation as set forth in its third policy letter: to avoid duplicative research, to provide incentives for generic sponsors to innovate and to make the conditions of the pioneer and generic drugs the same to the maximum extent possible.[30] This policy letter is consistent with CVM's historic generic animal drug policy. This history shows that CVM, like the human drug area where the data for DESI finalization applied to all identical, related, or similar drug products, has historically followed an analogous, broad approach to utilization of the data. Data required for a DESI upgrade or finalization is obtained from a variety of sources, such as revised labeling, public data, and the experience of practitioners. These findings were broadly applied because the applications originally contained a variety of data, *i.e.*, they were hybrids and the equivalent to drug products that were already on the market for a particular species, use, or indication. This policy letter is consistent with CVM's historic generic animal drug policy. As such, Pennfield has, at a minimum, approval as a paper NADA/hybrid application for all the claims

---

[25] *See e.g.,* North American Pharmacal, Inc. v. Dept. of Health, Educations, and Welfare, 491 F.2d 546 (8th Cir. 1973).

[26] H.R. 4982, House Report (Energy and Commerce Committee), No. 100-972(I), September 23, 1988. *See also* H.R. 4982, House Report (Judiciary Committee), No. 100-972(II), September 29, 1988 (both noting that § 101 of GADPTRA "specifically require[] a 'paper NADA' to be treated as an abbreviated application"). H.R. 4982 is an identical bill to S. 2843. *See* comments of Mr. Waxman, Congressional Record, House of Representatives, Proceedings and Debates of the 100th Congress, Second Session, Thursday, October 13, 1988. S. 2843 is the bill that eventually was signed into law as GADPTRA.

[27] Section 512(n)(5) of the FFDCA is the codification of the "paper NADA" concept. The section states that if an application contains particular information, including information on a pioneer drug's safety and effectiveness, "such application" shall be an application filed under § 512(b)(2). Section 512(b)(2), regarding abbreviated applications, in turn cross-references § 512(n).

[28] *See* March 20, 1991 seventh policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra.html.

[29] *See* March 20, 1991 seventh policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra.html, at 4.

[30] August 2, 1989 third policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra/html.

reviewed under the DESI process and subsequently found by FDA to be effective, no matter who supplied the data or when.

Finally, even if one ignored the nearly half-century of legal and administrative precedent that was reaffirmed by Congress, any period of three-year exclusivity[31] provided for by GADPTRA with respect to supplemental NADAs filed by AL Labs/Alpharma for that company's post-DESI claims would have since expired. The most recent supplement for Alpharma's BMD product, containing claims for replacement chickens, was published in the Federal Register in 1998.[32] Because it is now more than three years past this date of supplement approval, any period of exclusivity enjoyed by Alpharma would no longer exist. Because approvals already exist for multiple species, no additional data are scientifically required.

II. HISTORY OF BMD APPROVAL AS IT RELATES TO THE CURRENT CONTROVERSY

A. DESI Approval of Certain Claims for Effectiveness

BMD is an animal antibiotic that was first approved several decades ago,[33] prior to the 1962 Kefauver-Harris Drug Amendments ("1962 Amendments").[34] The 1962 Amendments, effective October 10, 1962, were significant to new drug approvals[35] 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"),[36] 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.[37] Section 507, which was added to the Act in 1945,[38] required FDA to certify batches of drugs composed in whole or in part of penicillin, without regard for whether the use was in humans

---

[31] FFDCA, § 512(c)(2)(F)(iii), codified at 21 USC § 360b(c)(2)(F)(iii).
[32] 63 FR 40824 (July 31, 1998).
[33] *See* 47 FR 42100 (September 24, 1982), corrected at 47 FR 51109 (November 12, 1982).
[34] PL 87-781, October 10, 1962.
[35] At this time, the new drug provisions applied to humans as well as other species.
[36] PL 90-399, July 13, 1969.
[37] *See* § 108(b)(2) of the 1968 Amendments, PL 90-399.
[38] 68 FR 47272, 47272 (August 8, 2003), citing PL 79-139.

or other animals.[39] This section operated much as a monograph and general rule, with the findings applicable to all identical, related, or similar drugs.[40]

On July 17, 1970, FDA published its response to the DESI Review on bacitracin products with and without penicillin conducted by NAS/NRC.[41] FDA generally concurred with the review, making a slight modification in the phrasing of language regarding claims for weight gains and feed efficiency.[42] The products addressed in the review were evaluated as (1) *probably effective* for growth claims in *poultry*, and (2) *probably not effective* for growth claims in *swine*, or for *therapeutic claims* (emphasis added).[43] Shortly thereafter, in October, 1970, FDA reevaluated the reports it had received in the DESI Review, with the Commissioner of Food and Drugs concluding that the products addressed in the review should instead be evaluated as (1) *probably effective* for growth claims in *poultry*, (2) *probably not effective* for *therapeutic claims*, and (3) *more information is needed* for the growth claim in *swine* (emphasis added).[44] Today, these DESI-reviewed claims are noted in 21 CFR § 558.76(d)(1)(i)-(ii). These claims include (1) BMD at 4-50 g/ton for *chickens, turkeys, and pheasants* for increased rate of weight gain and improved feed efficiency, and (2) BMD at 5-20 g/ton for *quail* not over five weeks of age for increased rate of weight gain and improved feed efficiency.[45]

---

[39] 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.

[40] 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 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 for animal drugs. "Identical, related, or similar" drugs are also mentioned in § 558.15.

[41] 35 FR 11531 (July 17, 1970); *amended at* 35 FR 15408 (October 2, 1970). This July 17 notice addressed products manufactured by a variety of companies, all of which contained bacitracin; however, some companies' products are stated to include bacitracin from zinc bacitracin or bacitracin from bacitracin methylene disalicylate. Just prior to this July 17 FR notice, a similar notice regarding "Certain Bacitracin Containing Drugs" that addressed products exclusively of Hoffmann-LaRoche Inc. was published. *See* 35 FR 10697 (July 1, 1970). All of these products contain bacitracin, but some state that they contain bacitracin from bacitracin methylene disalicylate. These multiple notices further illustrate some of the confusion that emanates from the DESI review process.

[42] The language regarding weight gains and feed efficiency was modified from "may result in faster gains and/or improved feed efficiency under appropriate conditions" to "For increased rate of weight gain and improved feed efficiency for (under appropriate conditions of use)." *See* 35 FR 11531, 11531-11532 (July 17, 1970).

[43] 35 FR 11531, 11531 (July 17, 1970).

[44] 35 FR 15408, 15408 (October 2, 1970). In the DESI report, the NAS/NRC stated that references regarding swine growth are inadequate, with more information needed. Therefore, the October 2 change in language may have only clarified what was intended to be stated in the July 17 Federal Register.

[45] These two subsections of § 558.76 are footnoted, which reads "These conditions are NAS/NRC reviewed and found effective. Applications for these uses may not require effectiveness data as specified by § 514.111 of this chapter, but may require bioequivalency and safety information." Note that the DESI review process concluded that the products reviewed were "probably effective" for growth claims in poultry, 35 FR 15408, 15408 (October 2, 1970), yet the footnote states "effective." This difference further illustrates the confusion surrounding the DESI review process.

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

In the early 1970's, safety issues arose regarding the possibility of antibiotic animal drugs contributing to bacterial strain resistance. FDA proposed to revoke the subtherapeutic uses of antibiotic, nitrofuran, and sulfonamide drugs that had been approved, unless drug sponsors conducted the necessary studies to resolve the issues. This effort led to the promulgation of § 135.109 in 1973, later redesignated § 558.15 in 1974.[46] Sponsors who conducted and submitted safety data were listed in (g)(1) as eligible for "interim marketing." Subsection (g)(2) listed those drug combinations permitted to be included in animal feed, when made from the Type A medicated articles that were listed in (g)(1).

For more than twenty years before the August 8, 2003 proposed rule, FDA had taken no steps to initiate the administrative process of finalizing § 558.15, including removing those sponsors who never submitted the studies, and listing those sponsors who had done so in the appropriate section in 21 CFR part 558, subpart B ("Specific New Animal Drugs For Use in Animal Feeds"). Therefore, while the phrase "interim marketing" now exists only as historical terminology, § 558.15 remains significant for those sponsors who are listed in the interim provision but not in part 558, subpart B. Until the next steps in the administrative process are completed, the sponsors, Type A medicated articles, and combinations that are listed in §§ 558.15(g)(1) and (g)(2) retain their the legal equivalent of NADAs approved through other mechanisms.

In the course of the rulemaking, FDA specifically addressed the issue of which companies held legal approvals. The Agency was found, during the course of the rulemaking, to lack the authority to authorize new companies from initially entering the market without a preexisting legal approval. According to the record, CVM reviewed the then-existing record and found that the companies listed had legal approvals, and the Agency codified those approvals. FDA's authority to promulgate binding legal substantive rules is indisputable.[47] FDA's authority to establish the legal classification of a product under its jurisdiction, whether a device, new animal drug, or other product, has been further established beyond dispute.[48] One primary reason that FDA used rulemaking for this matter was to obtain full public input to a process that had been complex and confusing. The Agency also wanted to provide clear public notice about the legal status of all the drug products then on the market and eligible for marketing; this is the function of regulations, and is also one of the functions served by regulations published under § 512(i) of the FFDCA.

---

[46] 37 FR 2444 (February 1, 1972) (proposed rule); 38 FR 9311 (April 20, 1973) (final rule); 38 FR 23942 (September 5, 1973) (final amended rule). The addition of § 558.15(g)(1) and (g)(2) was proposed in 39 FR 28393 (August 6, 1974) and finalized in 41 FR 8282 (February 25, 1976). § 135.109 originally applied only to antibiotic and sulfonamide drugs in the feed of animals; it was later amended to include the nitrofurans. *See* 38 FR 23942 (September 5, 1973). *See also* 68 FR 47272, 47273 (August 8, 2003) (indicating that redesignation of the section number occurred in 1974).

[47] *See e.g.,* National Nutritional Foods Ass'n v. Weinberger, 512 F.2d 688 (2d Cir. 1975).

[48] *See e.g.,* U.S. v. Article of Drug...Bacto-Unidisk, 394 U.S. 784 (1969).

That a listing in § 558.15 constitutes legal approval is clear from the decision in Hoffman LaRoche v. Weinberger.[49] In that case, the court held that FDA's policy of permitting the marketing of new drugs without obtaining an approval on a new drug application "contravenes the clear statutory requirement of preclearance mandated by 21 U.S.C. s 355 (1970)."[50] FDA recognized the scope of that holding by indicating in its final rule amending § 558.15 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."[51] Both AL Labs and Fermenta are currently listed in § 558.15(g)(1) as sponsors for BMD for use in chicken, turkeys, swine, and cattle for the use levels and indications for use listed in § 558.76. As a result, since sponsors listed in (g)(1) and (g)(2) have legal approval, FDA must provide a sponsor with an opportunity for an evidentiary hearing to resolve scientific disputes prior to any attempt to withdraw the approval of a product that is listed in § 558.15.[52] In addition, FDA bears the burden of coming forward with scientific and factual evidence to undermine the bases for the previous decisions.

C. September, 1982 DESI "Clean Up" Regarding BMD

In September, 1982, FDA published a notice that amended the animal drug regulations by withdrawing approval of certain claims found in NADAs filed by AL Labs and International Minerals & Chemical Corp. ("International") for use of bacitracin products in the feed and drinking water of chickens, turkeys, pheasants, quail, swine, and cattle.[53] Following the DESI Review of bacitracin with or without penicillin, as published in the Federal Register in 1970, AL Labs and International filed supplemental NADAs with final printed labeling. The companies also requested that FDA amend the regulations by removing claims reviewed by NAS/NRC found to be not effective or probably not effective, or those claims which were not supported by adequate and well-controlled studies. Thus, consistent with its standard implementation of the DESI program, CVM took the interim steps in 1982 to revise the labeling of claims associated with BMD for companies (AL Labs and International) with legal approvals who unilaterally and voluntarily submitted applications to the Agency. As specifically noted, the claims were upgraded to be effective through the use of supplemental data, information, and revised labeling. The notice however was not an NOOH and therefore does not even initiate the process to affect the approved claims of the legally approved BMD drug products set forth in § 558.15 for Pennfield. Approval of those claims can only be removed in accord with the due process procedures set forth in § 512 of the Act, which have only been initiated in August, 2003.

---

[49] 425 F.Supp 890 (D.D.C. 1975).
[50] *Id.* at 894.
[51] 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).
[52] *See, e.g.*, CVM Program Policy and Procedures Manual Guide 1240.3540, "Withdrawal of Approvals," and Guide 1243.3670, "Management of Formal Evidentiary Hearings, " *available at* http://www.fda.gov/cvm/index/policy_proced/ppindex.html.
[53] 47 FR 42100 (September 24, 1982), corrected at 47 FR 51109 (November 12, 1982).

D. Subsequent Filings by Some Holders of Approved NADAs

In its complaint, Alpharma alleged that FDA either unlawfully granted approval of Pennfield's NADA 141-137 for BMD, or unlawfully helped Pennfield make false representations that the company had FDA approval for NADA 141-137.[54] Alpharma took the position that since it was the only company that had filed and received approval for supplemental NADAs for the species, claims, and indications for use listed in § 558.76, it was therefore the only company that had lawful approval of all claims as listed in § 558.76.[55] Between 1981 and 1998, AL Labs and/or Alpharma filed ten supplements to its NADA 046-592.[56] In 1981, two additional post-DESI claims were transferred by FDA to AL Labs'/Alpharma's NADA 046-592 "for administrative reasons."[57] These claims involved the use of BMD with or without diethylstilbestrol (DES) for use in feedlot beef cattle.[58] While the use of BMD in combination with DES was later withdrawn from the regulations,[59] the use of BMD alone for feedlot beef cattle appears in § 558.76(d)(2).[60] Alpharma indicates that it has not authorized FDA to rely on safety and effectiveness data it has provided to FDA for BMD to use in the approval of BMD for Pennfield or it predecessors.[61] As a result, Alpharma alleges that "any manufacturer seeking to obtain approval for any of the 12 Post-DESI Claims must submit its own original data that meet the application submission requirements of the Animal Drug Amendments (statutory citations omitted)."[62]

The claims and indications that were sought by AL Labs/Alpharma fall within the language of claims that were reviewed by the DESI Review and findings, and the Agency's sanctioning of those claims constitute a part of the DESI review process. The DESI process includes a hybrid of data from all of the previously approved indications. It is unclear what types of data that Alpharma filed, but these have historically been found to apply to all DESI identical, related, or similar drug products. Under CVM's generic animal drug policy the data were applied to all species.[63] Even if under some legal theory Alpharma were entitled to legal exclusivity, the drug products in question are DESI effective and covered by GADPTRA. As such, any such legal exclusivity expired years ago. The labeling of the Pennfield drug products has legal approval of these claims. Under the statutory provisions of the FFDCA, the DESI upgrading data, including the data filed in any supplements, have been found to apply to Pennfield's drug products and claims. For these reasons FDA must set

---

[54] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 2.
[55] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 42.
[56] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 34 and Federal Register citations listed therein.
[57] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 33.
[58] 35 FR 9855 (June 16, 1970).
[59] 44 FR 39387 (July 6, 1979).
[60] Section 558.76(d)(2) is the only part of subsection (d) that refers to feedlot beef cattle.
[61] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 36.
[62] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 37.
[63] *See e.g.*, 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") and 21 CFR §§ 514.235 ("Judicial review") and 558.15 (both of which mention "identical, related, or similar" drug products). There is no identical counterpart to the human drug regulation § 310.6 in the animal drug regulations.

forth the scientific basis on which any such data are inapplicable to the claims in these products and show how they undermine the approvals. As a result, factual scientific questions exist. No DESI "finalization" can occur until FDA completes the due process hearing procedures provided to all holders of approvals.

III. CURRENT BMD CONTROVERSY

A. FDA's Administrative Posture[64]

In its August 8, 2003 NOOH, FDA appears to have taken the position that the Agency believes Pennfield only has lawful approval for the four DESI-reviewed claims listed in 21 CFR § 558.76(d)(1)(i)-(ii). Because the NOOH is broad and imprecise, it is not clear what FDA's position is on the two post-DESI claims for cattle.[65] According to FDA, because numerous amendments were made to § 558.76 over the years without appropriate corrections to the cross-reference to that section made in § 558.15, Pennfield only has approval for those claims/indications/species listed in § 558.76 at the time § 558.15 was first promulgated, in 1976.[66] Almost none of the precise claims from the 1976 version of § 558.76 appear in the most recent version of the CFR. As a result, FDA's position can be interpreted to mean that the Agency believes Pennfield only has lawful approval for the DESI-approved claims, and possibly for the two claims for feedlot beef cattle. We would expect the NOOH to be precise, so as to allow those parties invited to request a hearing, such as Pennfield, to precisely prepare its arguments in response. Despite this noted deficiency, Pennfield here presents its arguments for why the company has lawful NADA approval for NADA 141-137.

---

[64] The Agency notes that there are two outstanding NOOHs that are still pending, and that nothing in the August 8, 2003 NOOH "constitutes a bar to subsequent action to withdraw approval on the grounds cited in the outstanding NOOHs." 68 FR 47332, 47338-47339 (August 8, 2003). These two pending NOOHs are published at 42 FR 43772 (August 30, 1977) and 42 FR 56264 (October 21, 1977). These NOOHs cover proposals to withdraw approval of NADAs for all penicillin-containing premix products for use in animal feed, and for certain subtherapeutic uses of tetracyclines in animal feed. 68 FR 47332, 47339 (August 8, 2003).

[65] FDA does not make clear in its NOOH exactly which claims the Agency believes Pennfield has lawful approval for. However, based on the presence of the table containing the four DESI-approved claims (68 FR 47332, 47333 (August 8, 2003)), and no listing of any cattle claims in the NOOH, one might read the NOOH to imply that Pennfield is not entitled to make the claims for cattle listed in § 558.76(d)(2). However, the claims for cattle are listed in § 558.76 in 1976 and in § 558.76 today (2003). Therefore, although Alpharma appeared to believe in its complaint that it alone was entitled to the post-DESI cattle claims, this position may or may not comport with FDA's position in the NOOH. *See* complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶¶ 32-34, 38. (Note that Alpharma indicates it is the only sponsor of the two cattle claims listed in (d)(2) (*see* complaint, ¶ 38); however, (d)(2) does not list any sponsor numbers, unlike (d)(1). Subsection (d)(2) in the bacitracin zinc regulation, § 558.78, does happen to list Alpharma's sponsor code for the cattle claims, but this is not the case in the BMD regulation at issue here.) Notably, in the Stipulation and Order of Dismissal, the parties agreed that Pennfield does have approval to market its product for the two uses for feedlot beef cattle listed in § 558.76(d)(2). This appears to represent a change in position for Alpharma. *See* Stipulation and Order of Dismissal, A 16-17. Therefore, based simply on the complaint filed by Alpharma and the NOOH published by FDA, it would be unclear for which claims FDA believed Pennfield had lawful approval. While the Stipulation and Order of Dismissal tends to clarify the Agency's position on which claims it believes Pennfield can legally make, we would expect the Agency to clearly outline its position in the first instance. The NOOH should be sufficient on its face to provide the sponsor clear notice of FDA's position.

[66] 68 FR 47332, 47334 (August 8, 2003).

B. Pennfield's Arguments for Lawful NADA Approval

1. *Pennfield's predecessor in interest, Fermenta, is listed as a sponsor of BMD in § 558.15, and FDA's position that the Agency erred by not clarifying its regulatory provisions should not inure to Pennfield's detriment*

As discussed above, both Fermenta and AL Labs are today listed as sponsors in the "interim marketing" provisions of § 558.15(g)(1) for BMD for chicken, turkeys, swine, and cattle for the use levels and indications for use listed in § 558.76. The fact that this approval appears in an "interim marketing" provision is of no consequence. By virtue of the continued presence of the cross-reference to § 558.76 found in § 558.15, Pennfield is entitled to all of the claims that are found in the current version of § 558.76. Two additional species, pheasants and quail, were species that were considered under the DESI Review process; as such, claims for these species as approved in the DESI Review process may be made by any manufacturer.[67] Therefore, Pennfield has lawful approval for its NADA for the additional species of pheasants and quail as well.

FDA admits that the table in § 558.15(g)(1) is "misleading," unless one is aware of the changes that have occurred to both § 558.15 and § 558.76 over time.[68] Indeed, the majority of the claims that were listed in § 558.76 in 1976 are not listed in that section today. Even though FDA may believe that part of the underlying problem is the Agency's failure to update the regulations, such a circumstance should not inure to Pennfield's detriment. FDA is required to fulfill its obligations, and as the legislative history of the Animal Drug Amendments notes, one reason for requiring publication of approvals as regulations is to provide public notice of the approvals to avoid misunderstandings. In addition, as discussed above, the NOOH is unclear regarding which claims the Agency specifically believes Pennfield is making in error. The NOOH must be sufficient in and of itself to notify the intended parties as to what exactly FDA's position is.

Pennfield has legal approval under the FFDCA for all claims that were subject to the DESI Review. Approvals of these claims have never been withdrawn. Claims in that era were broad, and CVM never took further steps to finalize the DESI process that was initiated in 1982 (for companies holding legal approvals for BMD that did not voluntarily change their labeling) until August 8, 2003, twenty-one years later. The notices are only the first step in the lengthy legal and administrative processes. Under historic Agency policy and precedent, the findings of the DESI Review as upgraded are based on a hybrid of data, and the findings and labeling are available to all holders of legal approvals. For veterinary drugs part of the rationale is set forth in CVM's seventh policy letter implementing GADPTRA.[69]

---

[67] In 35 FR 11531 (July 17, 1970), FDA published its response to the DESI Review conducted by the National Academy of Sciences/National Research Council (NAS/NRC). Claims for "poultry" as a group were considered. 21 CFR § 558.76 (d)(1) footnotes the first two listings in the table, including certain claims for chickens, turkeys, pheasants, and quail, as those that were reviewed by NAS/NRC and found effective.

[68] 68 FR 47332, 47334 (August 8, 2003).

[69] March 20, 1991 seventh policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra/html.

Pennfield, with an historic approval, is legally permitted to make all of the claims in question. The Act sets forth the legal basis and procedures that FDA and CVM must follow to withdraw approval of Pennfield' s applications under § 512(d). The Center is required to set forth the scientific and legal bases for undermining its previous conclusions that the DESI findings and data are inapplicable to Pennfield's approvals. The Agency has done no more than state that somehow it made a mistake or misunderstood the facts. Such a glib assertion is not only untenable after more than a quarter of a century of extensive written and oral correspondence, meetings, and reliance by the industry, but it also fails to address the factual and scientific questions that exist because the data in existence supports all the claims in question. CVM is required by law to set forth how the data are inapplicable to all the individual claims in question.

Under FDA's unswerving precedents, and the plain language of GADPTRA that approvals can apply to all species and claims for the same drug,[70] as well as the fact that Pennfield's approvals cover all these claims under the DESI Review as finalized by the Agency and the hybrid data supplied by AL Labs is supported by the Agency's policies, Pennfield has approval for all these claims. CVM must set forth a scientific and legal basis that establishes the inapplicability of all data to support those claims. Until then, Pennfield has no legal obligation to provide any data.

Nevertheless, should FDA attempt to reverse half a century of Agency precedent, Pennfield will provide data, expert testimony, and other information in accord with the requirements of the Act as amended by GADPTRA that show that the data support its approval and all of the claims in question. Such a demonstration will require a formal evidentiary hearing to resolve the genuine and substantial issues of material fact.

2. *FDA's 1998 letter to BIV, Pennfield's immediate predecessor in interest, indicating the company had lawful approval of NADA 141-137*

Pennfield's contention that the company has lawful NADA approval is further supported and reaffirmed by a series of communications that took place in 1998 between FDA and BIV, which culminated in a letter from FDA stating that BIV had lawful approval for NADA 141-137 ("approved letter"). Such communication provides additional evidence that a sponsor's listing in § 558.15 is lawful approval for those claims/indications/species cross-referenced in § 558.76 as clarified under DESI and, of equal import, FDA's subsequent actions. If FDA had questions regarding the certification submitted by BIV in 1998, the Agency had ample opportunity to further clarify the administrative record prior to sending BIV the approved letter.

---

[70] *See e.g.*, FFDCA § 512(n)(1)(C)(ii) (codified at 21 USC § 360b(n)(1)(C)(ii)), § 512(n)(1)(D) (codified at 21 USC § 360b(n)(1)(D)) and § 512(n)(1)(E) (codified at 21 USC § 360b(n)(1)(E)). Bioequivalence data can apply to multiple species, and this NOOH applies to multiple species. Therefore, the Agency must come forward with evidence showing why the existing data do not apply to all species.

In the summer of 1998, FDA sent sponsor letters/certification requests to sponsors of animal drugs listed in § 558.15 for which FDA had an incomplete administrative record,[71] asking them to certify that they were entitled to be listed in § 558.15 prior to February 25, 1976, the date of publication of that section.[72] In pertinent part, FDA's letter states:

> The Agency will use the certification you provide along with the statement in the preamble to 21 CFR § 558.15 and other information in the Agency's files regarding the approval status of the new animal drug as the administrative record of the approval.
>
> This record would help ensure that Agency actions are consistent with the actual approval status of your new animal drug(s). Furthermore, this record will be used to respond to any judicial challenge to a new animal drug's approval status. While the Agency cannot guarantee that a court would find this record sufficient if the approval status is challenged, the Agency believes it can make arguments in light of the history surrounding new animal drugs in this class (e.g., the transition under the 1968 amendments, the long passage of time since the approvals were granted, etc.) to support a finding by a court that the record is adequate.[73]

BIV responded to this certification request with two letters to the Agency, dated September 18 and November 17, 1998.[74] In December, 1998, CVM responded to BIV's sponsor certification regarding NADA 141-137 and stated, in relevant part:

> In accordance with my letter, your certification will be used along with information in our files as the administrative record of an approval for NADA 141-137, which provides for a Type A Medicated Article, Noptracin MD-50 (bacitracin methylene disalicylate) for use for the indications and under the conditions of use specified in the labeling attached to your letter.
>
> The Agency will begin the work of codifying the approval via publication in the Federal Register. This task most likely will be accomplished as part of an action affecting a number of products currently listed in 21 CFR 558.15....*In the meantime, you may rely on this letter to verify the approved status of NADA 141-137* (emphasis added).[75]

---

[71] *See* July 29, 1998 letter from Stephen Sundlof to Dr. Donald Gable, Manager, Pharmaceutical Regulatory Affairs, BIV, attached as Exhibit D to Alpharma's complaint.
[72] 41 FR 8282 (February 25, 1976).
[73] *See* July 29, 1998 letter from Stephen Sundlof to Dr. Donald Gable, Manager, Pharmaceutical Regulatory Affairs, BIV, attached as Exhibit D to Alpharma's complaint.
[74] *See* September 18, 1998 and November 17, 1998 letters from Dr. Donald Gable to Stephen Sundlof. In the November 17, 1998 letter, the section for bacitracin zinc, § 558.78, is mistakenly referenced, instead of the correct section, § 558.76.
[75] December 17, 1998 letter from Stephen Sundlof to Dr. Donald Gable.

As a result of this sponsor certification and FDA "approved letter," Pennfield's previous argument, that listing in the "interim marketing" provision § 558.15 represents lawful approval for those claims listed in § 558.76, is reaffirmed.

FDA states, in the August 8, 2003 NOOH, that the Agency's record is still not clear in several respects. For example, the Agency acknowledges that BIV provided "good evidence," via a February 1969 product label, that the BMD product "was subject to transitional approval and the indications for which it was transitionally approved."[76] However, FDA has taken the position that it is now unclear regarding the meaning of the language used by BIV in the certification letters as to whether the company believed it had approval for the indications listed in § 558.76 as it appeared in 1976, or as that section appeared in 1998. The Agency also claims that additional labels were submitted "without any cover page or other explanatory notes," and indicates that FDA apparently does not know what to do with these labels.[77]

Pennfield believes that, if FDA had these questions in 1998, it had every opportunity to raise them with BIV prior to sending out the December 1998 "approved letter." The Agency did not do so. Furthermore, FDA now claims that its own December 1998 letter was confusing, since it referred to indications "specified in the labeling attached to [BIVI's] letter," but does not indicate to which labels FDA's letter is referring.[78] As argued in the previous section, Pennfield does not believe that it should now suffer because of FDA's apparent lack of clarity with its own administrative record. We acknowledge that the regulatory history of BMD is complex. However, Pennfield has submitted sufficient evidence through the years to provide a complete administrative record documenting full approval for all claims the company is currently making under NADA 141-137, both DESI and post-DESI.

As a matter of law, Pennfield approvals exist and are choate under the findings and language of §558.15. The basis for CVM's inquiry has never been clear. In effect it sought to covertly undo the public rulemaking that was conducted to clarify the legal status of the drug products in question. The language in the NOOH that confusion existed or exists is inconsistent with the rulemaking process. The administrative record in the rulemaking is incontestable. The approvals exist as a matter of law. These facts were reaffirmed through the extensive correspondence between BIV and CVM. An extensive factual record exists on the reaffirmation process. Twenty-seven years after the Agency decision was made through rulemaking, and five years after that decision was affirmed in a redundant process requiring submission and consideration of extensive information, the Agency states that it is confused. That statement has no credibility and raises serious legal questions about the Center's conduct in this matter. A statutory administrative process exists to resolve the questions that the Center now raises in its proposal to withdraw approval of Pennfield's applications, *i.e.*, the evidentiary hearing process. Serious factual questions exist about the Center's actions. Pennfield will provide evidence to dispute the Center's position, as well as raise issues about

---

[76] 68 FR 47332, 47334 (August 8, 2003).
[77] 68 FR 47332, 47334 (August 8, 2003).
[78] 68 FR 47332, 47334 (August 8, 2003).

the Center's proposed position to protect the existing approvals for its drug products. These are genuine and substantial issues of material fact that require a hearing for resolution.

3. *GADPTRA and CVM's implementing policy letters demonstrate that Pennfield has approval for all the claims in question*

The Generic Animal Drug and Patent Term Restoration Act, which was signed into law in November, 1988, formalized the approval process for generic animal drugs and provided patent protection for pioneer animal drug sponsors in much the same way that the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman") did for human drugs.[79] Prior to the passage of GADPTRA, generic animal drug approvals occurred through an administrative process, and only for those new animal drugs that had been approved before the 1962 Amendments. Prior to 1962, new drug applicants were only required to show that a drug was safe; efficacy was later demonstrated for these same drugs through the DESI Review process. As a result, generic drug applications were accepted for drugs that had been the subject of this "two part" review process - the initial demonstration by the sponsor of safety, followed later by the finding of efficacy in the DESI Review process. The DESI Review process and ANADA process replicate the human generic drug process. For post-1962 NADA's, GADPTRA was enacted to replicate the Hatch-Waxman Act.

In the legislative history of GADPTRA, two House subcommittee reports commented on § 101 of the act, and how it related to "paper NADAs."[80] This terminology has historically been used in the human new drug area, corresponding to applications approved under § 505(b)(2) of the Act. Paper NDAs were administrative predecessors to the process now codified in § 505(b)(2) and refer to those NDAs that rely on studies not conducted by or for the applicant to show safety and effectiveness, and for which the applicant has not obtained a right of reference or use from the person by or for whom investigations were conducted. In other words, a paper NDA relies on studies and information that are available in the public domain to support the applicant's demonstration of a drug's safety and effectiveness, or were not conducted by the applicant for the hybrid application. With respect to human drugs, FDA's "'Paper NDA' Memorandum" stated, for post-1962 duplicate NDAs, that

> [t]he NDA must be accompanied by published literature providing substantial evidence of effectiveness and appropriate evidence of safety for the claimed indication(s). Unpublished reports may also be submitted, when available and necessary....The compilation of published reports (preclinical and clinical) should be

---

[79] PL 98-417, September 24, 1984.

[80] H.R. 4982, House Report (Energy and Commerce Committee), No. 100-972(I), September 23, 1988. *See also* H.R. 4982, House Report (Judiciary Committee), No. 100-972(II), September 29, 1988 (both noting that § 101 of GADPTRA "specifically require[] a 'paper NADA' to be treated as an abbreviated application"). H.R. 4982 is an identical bill to S. 2843. *See* comments of Mr. Waxman, Congressional Record, House of Representatives, Proceedings and Debates of the 100th Congress, Second Session, Thursday, October 13, 1988. S. 2843 is the bill that eventually was signed into law as GADPTRA.

> the major papers in the literature relating to the drug and should be "balanced" and include those demonstrating negative as well as positive findings.[81]

Therefore, not all new human drug approvals have been based on original safety and effectiveness findings.

Similarly, the legislative history of GADPTRA shows that § 101 of the act was drafted to treat hybrid NADAs like paper NADAs.[82] Therefore, applications filed under § 101, hybrid applications, will be treated as § 505(b)(2) applications. Because of their similar treatment, neither ANADAs nor "paper NADAs" require full demonstrations of safety and effectiveness by unique data.[83]

Following the passage of GADPTRA, CVM issued a series of "policy letters" that explained CVM's thinking on a number of issues related to GADPTRA, and how the Center believed GADPTRA would be implemented in practice.[84] In the seventh policy letter, dated March 20, 1991, the Agency discusses these applications which it calls "hybrid applications." "Hybrids," like "paper NDAs" in the human drug area, are those approvals for new animal drugs in which sponsors may rely on safety and effectiveness data from other sources to show that the two drugs are equivalent. FDA proposed, in its letter, to accept these applications "for changes requiring the review of investigations conducted by or for the applicant, including changes in dosage form, strength, route of administration, and active ingredients (in a combination product), as well as new indications and new species."[85] In essence, this process is identical to the FFDCA § 505(b)(2) process. The function is to provide consistent, identical labeling. CVM indicated in this letter that these hybrids would rely on a listed animal drug's approval, along with data that is needed to support the change.

Moreover, this position complements CVM's historic position and its contemporary interpretation of the statute that the Agency is required under GADPTRA to avoid duplicative research and to make the conditions of use of the pioneer and the generic drugs the same to the maximum extent possible.[86] Here we have essentially identical pioneer products. Like the regulation of human drugs, where the data for DESI finalization applied

---

[81] 46 FR 27396 (May 19, 1981). *See also* 45 FR 82052 (December 12, 1980) (notice of FDA's consideration of a petition to withdraw the paper NDA policy as described in the staff memorandum, dated July 31, 1978, and to implement the policy (if at all) only after notice-and-comment rulemaking).

[82] *See* H.R. 4982, House Report (Energy and Commerce Committee), No. 100-972(I), September 23, 1988. *See also* H.R. 4982, House Report (Judiciary Committee), No. 100-972(II), September 29, 1988. Section 512(n)(5) of the FFDCA is the codification of the "paper NADA" concept. The section states that if an application contains particular information, including information on a pioneer drug's safety and effectiveness, "such application" shall be an application filed under § 512(b)(2). Section 512(b)(2), regarding abbreviated applications, in turn cross-references § 512(n).

[83] *See e.g.*, Upjohn Mfg. Co. v. Schweiker, 681 F.2d 480 (6th Cir. 1982).

[84] These policy letters are available on CVM's website at http://www.fda.gov/cvm/index/gadaptra/gadaptra.html. There are nine letters in all, dated between November 1988 and June 1995.

[85] March 20, 1991 seventh policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra/html, at 4.

[86] August 2, 1989 third policy letter from Gerald B. Guest, Director, CVM, and attached policy statements, *available at* http://www.fda.gov/cvm/index/gadaptra/gadaptra/html.

to all identical, related, or similar drug products, CVM has historically followed an analogous, broad approach to utilization of the data. Data required for a DESI upgrade or finalization is obtained from many sources, including revised labeling, public data, and the experience of practitioners. These findings were broadly applied because the applications originally contained a variety of data, *i.e.*, they were hybrids and the equivalent to drug products that were already on the market for a particular species, use, or indication.

The policy letters are consistent with CVM's historic policy and state that the Agency, as it has for almost fifty years, has treated these drug products as a class.[87] The data have been applied as a whole across the class, in part since the drug products were originally marketed under an antibiotic public rule. One piece of data cannot be segregated from the foundation of data that has been used to support the basic conclusion that the drug products of this type are safe and effective for the claims in question. Congruent labeling of all identical or similar drug products of this type has always been considered by the Agency the best public policy, especially when the basic data were generated by many companies, experts, and the Agency's expertise, and only when considered as a whole provided the basis for the findings of safety and effectiveness. These points establish that Pennfield's application is approved for all the indications in question and that the Center's correspondence reaffirms these approvals under the provisions of GADPTRA for all of the claims. Furthermore, FDA's attempts to eliminate or segregate the data raise factual and scientific questions. CVM must set forth the scientific bases for the inapplicability of the data to Pennfield's approvals. Only then must Pennfield rebut CVM's position, and the data and evidence necessary for rebuttal can run the panoply of scientific data. A cavalier assertion that novel adequate and well-controlled field investigations are required cannot be raised as a legal hurdle, especially since the drug products approved under the safety and effectiveness standard of the FFDCA only require one study for proof of effectiveness.

For all the foregoing issues, genuine and substantial issues of material fact exist that require a hearing for resolution. Pennfield will provide data and information that meet the applicable legal standards to support its position in this matter.

4. *Any three-year exclusivity period was enjoyed by AL Labs/Alpharma has since expired*

GADPTRA provided three-year exclusivity periods for supplements containing "substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the supplement and conducted or sponsored by the person submitting the supplement."[88] Alpharma has filed a series of supplements for its BMD product, dating from 1981-1998;[89] whether any of these supplements contained data that permit them to qualify for exclusivity are factual questions

---

[87] *See e.g.*, 21 CFR § 310.6, 21 CFR § 514.235, and 21 CFR § 558.15.
[88] FFDCA, § 512(c)(2)(F)(iii), codified at 21 USC § 360b(c)(2)(F)(iii).
[89] Complaint, Alpharma, Inc. v. McClellan, Case # 8:03-cv-01406-PJM, May 13, 2003, at ¶ 34, and references cited therein.

that require hearings to resolve. Due process further mandates that these data be provided to Pennfield in order to address these issues. But as a practical matter the issues are moot. Since this three-year period of exclusivity applies only to those supplements approved after the date of enactment of GADPTRA (November 16, 1988), any three-year exclusivity that Alpharma would have been granted under this provision would only apply to a small subset of its total supplements. Furthermore, since the most recent supplement was published in the Federal Register in 1998, any exclusivity that did at one time apply to Alpharma's approvals no longer exists. As a result, CVM is not barred from approving an application submitted under § 512(b)(2)[90] of the FFDCA for a change approved in the supplement.

No data are required because, as shown by the very fact that notices have been published, the DESI findings were never finalized for holders of approvals who did not surrender their rights and labeling in 1982. Accordingly, the Agency precedent applies the existing data and general findings to all DESI-reviewed drugs, including those of Pennfield. Moreover, even if data were submitted and qualified for three years of market exclusivity, those periods have long since expired. As such, the matter is moot.

C. Pennfield's Additional Arguments Regarding FDA's NOOH

1. Legal Framework

The statutory and due process requirement for an NOOH is to provide the affected parties with notice of the legal and scientific issues that are in dispute about the approved applications. The issues in dispute must be adequate to serve as a basis for withdrawing approval of the applications if not resolved. The NOOH also must meet the due process requirement of adequacy of the issues and the facts that form the basis for the proposed agency action.

The Center can provide adequate general or specific notice of the issues in dispute. A general notice should set forth the basic scientific and legal issues that are in dispute and explain why failure to resolve these issues can lead to the withdrawal of the approval of the applications in question. Specific notice should then set forth the precise legal and factual issues in dispute to narrow and clarify the issues in dispute. FDA has historically used specific notice as a mechanism for framing the precise issues to administer administrative summary judgment in its favor.

Conceptually the issues can be framed or narrowed by a comprehensive explanation of the issues in the NOOH that provides the legal, scientific and factual basis for the standards and their applicability to the matter.[91] Additionally, decades ago, the agency was able to utilize the establishment of regulations that define the statutory standard in question as specific notice and a threshold barrier to providing a hearing to the affected holder of the approval.[92] Neither approach is viable here.

---

[90] Codified at 21 USC § 360b(b)(2).
[91] Hess & Clark, Division of Rhodia, Inc. v. FDA 495 F.2d 975 (D.C. Cir. 1974).
[92] Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609 (1973).

Without a rulemaking procedure to establish a legal threshold, the courts have uniformly rejected the agency's ability to create a standard in a notice and frame issues for administrative summary judgment.[93] The ability of the agency unilaterally to establish standards in a notice as a prelude to administrative summary judgment is today fundamentally unsound in the normal course of events and especially in this matter.

The Center's ability to impose a regulation, *e.g.* 21 CFR § 514.117, defining adequate and well controlled studies, as a barrier to a hearing also has no validity in this matter for legal, factual and scientific reasons. FDA's unilateral ability to impose a standard without a hearing is a vestige of a different era. The courts have imposed such severe limitations on the agency's actions[94] that such an action in this case is legally impossible.

The Center's notice is totally confusing. Moreover, the notice mentions facts, correspondence, reviews of studies, consideration of data, data, and more that are not in the public record, and they are not explained in sufficient detail to permit specific refutation. Extensive administrative discovery is required.

The issues in this matter concern that the quantum and quality of data, if any, that are necessary to provide evidence of effectiveness of approved claims for drug products that have been involved in the DESI review process for the past thirty years. Claims for all species and a variety of strengths of the drug were found to be effective and applicable to all identical, related, or similar drug products. Claims were elevated to effective on the basis of revisions in labeling, literature, scientific evidence, scientific review, agency expertise, and individual data. These data were considered as a whole. Pennfield must have the opportunity to review these data in order to defend its approvals on factual and due process grounds.

Further since the initiation of the DESI review process Congress has twice amended the FDC Act to revise the data required to show effectiveness for an application. Only one adequate and well-controlled field investigation is required to show effectiveness, and generic/hybrid and other applications can be approved for multiple species and claims without additional adequate and well-controlled studies. Data can be utilized among the species, claims and strengths. CVM also appears to be revising its historic practice of handling data in these matters.

FDA 's ability to impose novel legal standards or scientific questions in hearing process requires full scientific and legal vetting and debate. Moreover, in some situations rulemaking may be required to revise that legal or scientific standard.[95] FDA cannot merely

---

[93] *See e.g.,* American Cyanamid Co. v. FDA, 606 F.2d 1307 (D.C. Cir. 1979). *See also generally,* Hess & Clark, Division of Rhodia, Inc. v. FDA 495 F.2d 975 (D.C. Cir. 1974).

[94] *See e.g.,* SmithKline Corp. v. FDA, 587 F.2d 1107 (D.C. Cir. 1978) and Masti-Kure Products Co., Inc. v. Califano, 587 F.2d 1099 (D.C. Cir. 1978).

[95] *See e.g.,* Ford Motor Co. v. FTC, 673 F.2d 1008 (9th Cir. 1981), and Brown-Forman Distillers Corp. v. Mathews, 435 F.Supp. 5 (W.D. Ky. 1976).

assert that some standard exists, assert that it has followed that course of action in the past and refuse a hearing. FDA cannot in a notice revise the agency's actions for process DESI claims. It cannot impose a new standard. It must provide in the record that basis for each proposed action. Then a hearing is required to provide due process in this matter.

2. *FDA has the burden of providing adequate notice of any purported lack of approval, and the scientific, legal, and factual basis therefore*

a) Legal basis of approval

By virtue of the language used in the NOOH, FDA's actions can be interpreted as an attempt to shift to Pennfield the burden of coming forward with evidence indicating that the company has obtained lawful approval for its BMD product, although the exact nature of what Pennfield is expected to prove is unclear. According to the Agency, "[w]e are not aware of any additional approved indications beyond those listed in the original § 558.76 from 1976 for Pennfield Oil Co.'s product. *If the sponsor has additional information on the other approved indications, such information should be provided to FDA during this administrative process* (emphasis added)."[96] This language misstates the legal basis for Pennfield's position and suggests that FDA is unaware of Pennfield's legal approval for all claims considered as part of the DESI review which the agency is only now beginning to finalize.

However, later in the NOOH, FDA frames this issue differently, instead indicating that the issue is really one of efficacy:

> The ground for the proposed withdrawal is that new information about the drug products, such as that provided by the NAS/NRC reviews, evaluated together with the evidence available at the time of approval, show there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[97]

Entitlement to make claims and the efficacy of claims one is entitled to make are two very different legal and scientific issues. If FDA had questions regarding the efficacy of claims covered by the DESI, then the Agency should be calling Alpharma's claims into question in this same NOOH; the Agency does not take this action. We interpret FDA's position to ultimately be one of Pennfield's entitlement to make such claims, couched in efficacy terms. As such, FDA appears to be inappropriately conflating the two issues.

In Hess & Clark, Division of Rhodia, Inc. v. FDA,[98] the U.S. Court of Appeals, District of Columbia Circuit explained the significance of clarity of an NOOH as it relates to FDA's summary judgment procedures:[99]

---

[96] 68 FR 47332, 47334 (August 8, 2003).
[97] 68 FR 47332, 47339 (August 8, 2003). These ground for withdrawal are found at § 512(e)(1)(C) of the Act, codified at 21 USC § 360b(e)(1)(C).
[98] 495 F.2d 975 (D.C. Cir. 1974).

> When the FDA issues a Notice of Opportunity for Hearing, its summary judgment procedures are available if the requesting party fails to raise material issues of fact. For that reason, the contents of the response are of critical importance, and the need for and importance of the response in turn enhances the significance of the notice given to the adverse party. *In order to be adequate, such notice given by the agency to an adverse party must contain enough information to provide the respondent a genuine opportunity to identify material issues of fact.* This is needful to provide the "due notice and opportunity for hearing" required by the Act (emphasis added).[100]

Furthermore, Hess & Clark addressed the fact that FDA is responsible for coming forward with the initial evidence that a drug is not safe before the sponsor needs to provide evidence of safety:[101]

> The statute plainly places on the FDA an initial burden to adduce the "new evidence" and what that new evidence "shows." *Only when the FDA has met this initial burden of coming forward with the new evidence is there a burden on the manufacturer* to show that the drug is safe. Only at this later stage must the manufacturer produce "adequate tests" of safety (emphasis added).[102]

Taken together, these concepts illustrate that the Agency is responsible for proving why a drug is not entitled to be marketed. Not until the Agency has met this burden, must the sponsor must provide rebuttal information to show why the drug is safe/effective. CVM set forth its basis that no legal approval exist for the DESI reviewed claims as set forth above in detail. Factual evidence exists that disputes clearly the Center's position, and as the required discovery proceeds even more disputed evidence will be shown. A hearing is necessary to resolve these matters.

b) Scientific evidence support the DESI-reviewed claims

Above, we have laid out the historic and factual basis upon which FDA has reviewed and considered evidence applicable to claims subject to the DESI review process. As noted above, the Center's notice is totally confusing. Moreover, the notice mentions facts, correspondence, reviews of studies, consideration of data, data, and more that are not in the public record, and not explained in detail that permits specific refutation. Extensive administrative discovery is required.

---

[99] FDA's summary judgment procedures were previously validated in Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609 (1973). These procedures are found at 21 CFR § 514.200 ("Contents of notice of opportunity for a hearing").

[100] 495 F.2d at 983.

[101] We are aware that Hess & Clark was a case dealing with the safety of a drug, not the efficacy of a drug. However, except with respect to what the "new evidence" may constitute, the statutory provisions allowing for withdrawal of a drug by the Secretary for safety and efficacy reasons are similar, *i.e.*, both require that the Secretary base his decision on new evidence/new information plus evidence available to him when the application was approved. *Compare* § 512(e)(1)(B) (safety; codified at 21 USC § 360b(e)(1)(B)) with § 512(e)(1)(C) (efficacy; codified at 21 USC § 360b(e)(1)(C)).

[102] 495 F.2d at 992.

The issues in this matter concern that the quantum and quality of data, if any, that are necessary to provide evidence of effectiveness of approved claims for drug products that have been involved in the DESI review process for the past thirty years. Claims for all species and a variety of strengths were found to be effective and applicable to all identical, related, or similar drug products. Claims were elevated to effective on the basis of revisions in labeling, literature, scientific evidence, scientific review, agency expertise, and individual data. These data were considered in to. Pennfield must have the opportunity to review these data in order to defend its approvals on factual and due process grounds.

FDA's attempt in the NOOH to impose the adequate and well-controlled studies standard represents a change in the historic approach and the imposition of a novel standard in the NOOH, which is analogous to the situation in Hess & Clark[103] and American Cyanamid.[104] As such, factual questions exist about the applicability of the data to a variety of species and claims. Nonetheless, Pennfield will provide evidence from adequate and well-controlled studies, including appropriate data equivalent to that used by the Center to set forth its position to support all the claims for BMD, as these claims were broadly used in the DESI review, to support its approvals. For these reasons, genuine and substantial issues of material fact exist that require a hearing for resolution.

3. FDA cannot use an assertion of mistake to circumvent the NOOH process and due process

FDA alludes in several instances in the NOOH to the notion that the Agency's mistake is in part the reason for the confusion with respect to the approval status of NADA 141-137.[105] Pennfield calls into question the ability of FDA to base its decision to issue the NOOH, at least in part, on the carelessness of the Agency's own actions. Pennfield has approval under the FFDCA, and the approval covers claims reviewed in the DESI process. Due process and the NADA withdrawal of approval process provide the only way to address issues in dispute or bald assertions. Such truncated action is extraordinary relief as it has only been upheld one time. This case reaffirms Pennfield's right to a hearing involving the so-called "mistake." In American Therapeutics, Inc. v. Sullivan,[106] FDA approved the plaintiff's ANDA by letter, and less than two months later voided the approval by sending a rescission letter without a hearing, claiming that an "inadvertent mistake" had been made (although FDA indicated to the company that, if the Agency ultimately denied the ANDA, the company would receive a subsequent hearing).[107] The court first of all noted that "[t]here is no regulation or statutory provision that contemplates rescission of an approval issued by mistake." The court then proceeded to state that:

---

[103] 495 F.2d 975 (D.C. Cir. 1974).
[104] 606 F.2d 1307 (D.C. Cir. 1979).
[105] The Agency uses such phrases as "was not updated" and "the table is misleading." 68 FR 47332, 47334 (August 8, 2003).
[106] 755 F.Supp. 1 (D.D.C. 1990).
[107] 755 F.Supp. at 1.

> Here, an agency *almost immediately discovers its own error* in awarding approval of a drug which the statute directed should not be awarded based on facts available at the time.
>
> FDA is entitled to some deference when its action is examined. This was a good faith mistake *promptly discovered and corrected*, nothing more (emphasis added).[108]

This case illustrates that FDA's ability to correct its mistakes is available only in a truncated manner in limited circumstances, namely, when the error is both discovered quickly and corrected quickly. In American Therapeutics, the amount of time elapsed between approving the ANDA and the rescission was mere weeks; in Pennfield's case, FDA's "approved letter" was sent in 1998, now approaching five years ago. Because the present situation is clearly outside of the time frame that occurred in American Therapeutics, Pennfield questions the ability of FDA to use its own mistake as a basis for such an action. Genuine and substantial issues of fact exist about the alleged "mistake." A comprehensive record exists. More evidence obviously exists within the Center. Pennfield disputes the Center's assertion that "mistakes" were made. Evidence will be submitted to support a hearing on this matter.

4. Questions surrounding the veracity of FDA's claims in the NOOH regarding labeling are raised

In the NOOH, FDA indicates that the Agency is not clear as to the meaning of two labels supplied to FDA by BIV on December 9, 1998, as "[t]hese are in the product's current NADA file, although without any cover page or other explanatory notes."[109] We call into question whether this lack of nomenclature is due to actions taken by Pennfield (BIV) or by FDA. Regardless of this answer, Pennfield questions the Agency's use of this information as a basis, at least in part, for its decision to issue the NOOH. At any rate, FDA's "approved letter" to BIV did not issue until December 17, 1998, eight days following this submission of labels. As we have argued above, if FDA was confused as to the information submitted, it could have clarified this with the company prior to issuance of the letter confirming approval of NADA 141-137.

D. Pennfield's Position on the Proposed Rule to Remove Obsolete and Redundant Regulations (21 CFR §§ 510.515, 558.15)

1. Removal of 21 CFR § 510.515

As FDA outlines in its proposed rule, § 510.515 contains exemptions for some antibiotics used in animal feeds. These exemptions arose since § 507, which provided certification of batches of drugs composed of penicillin (and later other antibiotics), provided for FDA to issue regulations that exempted those batches from batch certification requirements.[110] Under GADPTRA, however, antibiotic certification provisions were removed from the Act. Thus, as FDA states, the purpose of § 510.515 "was rendered

---

[108] 755 F.Supp. at 2.
[109] 68 FR 47332, 47334 (August 8, 2003).
[110] 68 FR 47272, 47272-47273 (August 8, 2003).

obsolete with the enactment of GADPTRA."[111] Pennfield agrees that § 510.515 is an obsolete regulation, and does not oppose its removal from the CFR.

2. Removal of 21 CFR § 558.15

The Agency would remove § 558.15 "because it long ago fulfilled its stated purpose of requiring sponsors to submit data regarding the subtherapeutic use of antibiotics on the market at the time of its publication."[112] Furthermore, the Agency outlines the development of a draft guidance for industry entitled "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern (#152)."[113] FDA concludes that, therefore, even if § 558.15 is removed from the regulations, studies will still be required to assess consequences of using antimicrobials in animals that are used for food-producing purposes.[114]

FDA also comments that "the removal of § 558.15 is not intended to have a substantive effect on the products subject to the section's interim marketing provisions," as most products listed in § 558.15 are already codified elsewhere in part 558, subpart B.[115] Pennfield's predecessor in interest, Fermenta, is currently listed in § 558.15. FDA's NOOH would propose to not list Pennfield in § 558.76 beyond those claims for which FDA believes Pennfield has provided evidence of effectiveness. As Pennfield believes it currently has lawful NADA approval for all of the claims/indications/species listed in § 558.76, FDA's actions would result in the company being listed in that section for fewer than all of the claims/indications/species for which we have approval.

Therefore, Pennfield objects to the proposed rule to remove § 558.15 until the issues in the NOOH are addressed. If Pennfield is properly acknowledged in § 558.76, showing it has lawful approval for all DESI and post-DESI claims, then the company does not oppose removing § 558.15. However, if the Agency determines that Pennfield does not have lawful approval to be listed in § 558.76 for all claims, both DESI and post-DESI, then the company opposes removal of § 558.15. Our listing (Fermenta) in § 558.15 provides evidence of our lawful approval; removal of that section, without appropriate acknowledgement in § 558.76, would result in lack of recognition in the regulations of the approval that Pennfield currently has.

IV. CONCLUSION

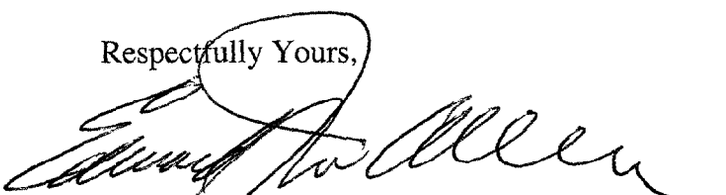
For the reasons outlined above, Pennfield has lawful approval for NADA 141-137 for Pennitracin MD 50-G, a BMD product, for those claims listed in § 558.76 as clarified under DESI and, or equal import, FDA's subsequent actions. Substantial evidence will be submitted to demonstrate that genuine and substantial issues of material fact exist that requires a hearing for resolution. Any confusion over the issues must be addressed in a

---

[111] 68 FR 47272, 47273 (August 8, 2003).
[112] 68 FR 47272, 47274 (August 8, 2003).
[113] *Available at* CVM's Published Guidance Documents page, http://www.fda.gov/cvm/guidance/dguide152.pdf.
[114] 68 FR 47272, 47274 (August 8, 2003).
[115] 68 FR 47272, 47275 (August 8, 2003).

hearing. Therefore, Pennfield respectfully requests a hearing on these matters. As illustrated above, although we believe the Agency has not provided adequate notice and has not met its burdens of going forward, we will, in accordance with the NOOH and regulation, provide additional materials, including the data and analysis upon which this request for a hearing relies, by October 7, 2003.

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