DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

RONALD R. FULLER, D.V.M.

FROM RECEIVING INVESTIGATIONAL NEW ANIMAL DRUGS

REPORT OF THE PRESIDING OFFICER

INTRODUCTION

This hearing was held under 21 CFR Part 16 to consider the Center for Veterinary Medicine's proposal to disqualify Ronald R. Fuller, D.V.M., from receiving investigational new animal drugs. The Center for Veterinary Medicine, hereinafter referred to as "the Center," charged that Dr. Fuller repeatedly or deliberately submitted false information to the sponsor of a clinical trial on the use of tablets in dogs. The Center made six allegations in support of this charge:

(1) Interviews with 22 of 40 owners of dogs supposedly treated during the study show that 10 owners denied that their animals were

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injured or treated as reported by Dr. Fuller, and 8 owners did not remember the injuries or treatment for their dogs.

(2) The authenticity of the case report forms is suspect because 39 of 43 case reports involved traumatic injuries, and the nature of the trauma was similar in the reports. The owners were unaware of any source of trauma for their dogs.

(3) There was inadequate information in medical records to support the information Dr. Fuller reported on the case report forms, including the animals's initial conditions, periods of confinement, drug used or time or dosage, and clinical observations. Furthermore, the study data in the medical records for two animals conflicted with the information on the case report forms.

(4) Only two hospital records show that the animals were part of the trial.

(5) Dr. Fuller altered medical records after they were initially reviewed by FDA investigator Lochner and admitted that he did so to Mr. Lochner.

(6) Concomitant drug use was not reported on case report forms.

See Letter from Melvin S. Drozen, Esq. to Ronald R. Fuller, D.V.M., March 4, 1987. Consequently, the Center argued that Dr. Fuller should be declared ineligible to receive investigational new animal drugs.

The hearing on this matter was held on March 31, 1987. Although the agency made every reasonable effort to accommodate Dr. Fuller and to ensure that the hearing was scheduled for a date when he could attend, Dr. Fuller informed my office on the evening of March 30, 1987 that his presence at the hearing would depend on his ability to retain a certain attorney. Dr. Fuller stated that he would attend the hearing if he retained a specific attorney; if he could not get the attorney to represent him, he would not appear. The agency, therefore, did not know whether Dr. Fuller would attend his own hearing until he failed to appear at the scheduled hearing time and place. I will briefly summarize the history of this proceeding:

(1) On March 11, 1986, the Center for Veterinary Medicine, through Dr. William B. Bixler, informed Dr. Fuller of the allegations

against him and invited him to schedule a conference with FDA officials, to enter a consent agreement, or to seek a hearing pursuant to 21 CFR Part 16. No reply was received.

(2) In a letter dated August 4, 1986, John M. Taylor, then-Acting Associate Commissioner for Regulatory Affairs, formally notified Dr. Fuller of an opportunity for a regulatory hearing to determine whether he would be entitled to continue to receive investigational new animal drugs. Mr. Taylor's letter stated that a request for a hearing would have to be made to Mrs. Mary M. Lyda within 10 working days after receipt of his letter. If no response was received, a decision would be made solely on the basis of the facts on hand. Mrs. Lyda's memorandum of telephone conversation indicates that Dr. Fuller did attempt to contact her on August 19-20, 1986.

(3) On August 22, 1986, Mrs. Mary M. Lyda informed Dr. Fuller about regulatory hearings and again asked whether he wished to have a regulatory hearing. Mrs. Lyda sent information on regulatory hearings to Dr. Fuller on August 25, 1986, and asked that he inform her of his decision within 10 days of receipt of the materials. Mrs. Lyda's records indicate that Dr. Fuller tried to call Mrs. Lyda on September 12, 1986 - 18 days after she sent the materials to him.

(4) In the course of a telephone conversation on September 16, 1986, Dr. Fuller informed Mrs. Lyda of his desire to have a regulatory hearing. Mrs. Lyda accepted his verbal request and advised him that a written request would have to be submitted. On October 1, 1986, FDA received Dr. Fuller's note, dated September 16, 1986, confirming the telephone conversation.

(5) On December 12, 1986, Mr. Philip L. Chao, of my staff, contacted Dr. Fuller to schedule a hearing. Dr. Fuller indicated that he would be unable to attend a hearing until February. Mr. Chao was later called by Dr. Dr. stated that Dr. Fuller had called him about the hearing, and that he felt that an agreement could be reached between Dr. Fuller and the Center for Veterinary Medicine, FDA. On the basis of that phone call, Mr. Chao invited Dr. Fuller to call Melvin Drozen, Esq., the attorney for the Center, to explore a settlement.

(6) From December 15-22, 1986, Dr. Fuller and Mr. Drozen attempted to reach an agreement but were unable to do so.

(7) On December 29, 1986, Mr. Chao again called Dr. Fuller to schedule a hearing date. Dr. Fuller tentatively agreed to February 11-12, 1987, but indicated that he would have

to check these dates with other parties whom he declined to identify. Dr. Fuller stated that he would reply by December 30, 1986. No reply was received.

(8) On December 31, 1986, Mr. Chao again called Dr. Fuller to confirm the February hearing dates. Dr. Fuller stated that he was unable to contact his parties and would reply by January 5, 1987. No reply was received.

(9) On January 6, 1987, Mr. Chao called Dr. Fuller to confirm the February 11-12, 1987 hearing dates. Again, Dr. Fuller stated that he was unable to contact his parties and would reply by January 9, 1987.

(10) On January 9, 1987, Mr. Chao called Dr. Fuller to confirm the February 11-12, 1987 hearing dates. Dr. Fuller tentatively agreed to the dates but again indicated that he would have to check with other parties to see if the dates would be acceptable to

them. Dr. Fuller rejected February 13, 1987 because of a prior commitment.

(11) In a letter dated January 16, 1987, I formally notified both parties that the hearing would be held on February 11-12, 1987 in room 4A-35 of the Parklawn Building, 5600 Fishers Lane, Rockville, MD. The hearing was set to begin at 8:00 a.m. Copies of all prior telephone conversations with Mr. Chao were attached along with copies of the pertinent FDA regulations.

(12) On January 23, 1987, Dr. Fuller called Mr. Chao to inquire whether the hearing was still scheduled for March 11-12, 1987. He stated that he had always understood the hearing to be scheduled for March rather than February, and that the February dates were unacceptable because of a scheduling conflict.

(13) On January 28, 1987, Dr. Fuller called Mr. Chao to inquire when the hearing would be scheduled. However, Dr. Fuller did not agree to any of the proposed dates.

(14) On February 3, 1987, I invoked my authority as presiding officer to set a date for the hearing. I presented the parties with two dates, March 3-4, 1987 or March 31-April 1, 1987, and asked the parties to select a date within 10 days of my letter. Mr. Drozen replied on February 4, 1987, and indicated that both dates were acceptable. Dr. Fuller failed to reply, and Mr. Chao had to contact him on February 17, 1987. The hearing was set for March 31-April 1, 1987. I later denied a request by Dr. Fuller to postpone the hearing.

(15) On the afternoon of March 30, 1987, Dr. Fuller again contacted Mr. Drozen and Mr. Chao to request a postponement because he had been unable to contact a certain

> Washington-area attorney. I denied this request because Dr. Fuller had been on notice regarding a regulatory hearing since March 1986 and had been advised on numerous occasions over a period of several months to consider retaining counsel but had consistently declined to retain counsel. When his request for a postponement was denied, Dr. Fuller stated that although he could be present at the hearing, he would not attend the hearing unless he could secure the services of a specific Washington-area attorney. If was able to retain the attorney, he would appear at the hearing.

Based on this record, I found that it was appropriate for the hearing to proceed even though Dr. Fuller ultimately chose not to attend. As stated earlier, Dr. Fuller's attendance for his own hearing was uncertain until he failed to appear at the scheduled hearing time and place.

Dr. Fuller not only declined to appear, but he also did not submit any written materials for my consideration. The

Center presented two witnesses. The first, Dr. Virginia Dobozy, a veterinary medicine officer in the Center, testified about her review of Dr. Fuller's case report forms and the entries in those forms. The second, Mr. Frederick Lochner, a FDA investigator, testified about his inspection at Dr. Fuller's animal hospital and his review of the medical records for the study. Mr. Lochner also testified about Dr. Fuller's actions during the inspection and about the affidavits from animal owners.

The remainder of this report consists of my findings and conclusions based on the full administrative record of the hearing, including the hearing transcript and exhibits. Copies of these materials are attached.

THE REGULATORY FRAMEWORK

FDA's regulation governing the conduct of investigational new animal drug studies (21 CFR 511.1) states that "[w]henever the Food and Drug Administration has information indicating that an investigator has repeatedly or deliberately failed to comply with the conditions of these exempting regulations or has submitted false information either to the sponsor of the investigation or in any required report," the Center for Veterinary Medicine will provide the investigator with the

opportunity to explain the matter in an informal conference. 21 CFR 511.1(c)(1). If the Center does not accept the investigator's explanation, the investigator will be given the opportunity for a regulatory hearing.

The regulation also states that the Commissioner will inform an investigator that he or she is ineligible to receive investigational new animal drugs if:

> after evaluating all available information including any explanation and assurance presented by the investigator, the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this section or has repeatedly or deliberately submitted false information to the sponsor of an investigation and has failed to furnish adequate assurance that the conditions of the exemption will be met....

21 CFR 511.1(c)(2). In the present case, the only question presented by the Center is whether Dr. Fuller "repeatedly or deliberately submitted false information" to the study sponsor.

ANALYSIS AND DISCUSSION

In preparing my report, I have carefully reviewed the information presented in the administrative record and

regulatory hearing.[1] Based on the totality of the evidence and testimony, I conclude that Dr. Fuller repeatedly submitted false reports to the sponsor of the study and, therefore, violated 21 CFR 511. I have reached this conclusion because:

(1) The affidavits from the owners of the dogs supposedly enrolled in the study fail to support the case report entries. The owners either denied or could not remember any injury suffered by or any treatment given to their animals, whereas the case report forms frequently noted the cause of injury.

(2) The medical records for the animals supposedly enrolled in the study also failed to support the information in the case report forms. Although Dr. Fuller stated in his affidavit that he simply entered information on the case report forms rather than the medical records, the medical records contain entries that are inconsistent with the dates during which the animals were supposedly participating in the study.

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[1] Aside from an affidavit which was taken by Mr. Lochner, Dr. Fuller has consistently declined to present any explanation, statement, or assurance regarding his conduct during the study. Therefore, the bulk of the administrative record was submitted by the Center.

(3) While some medical records bear a notation, which Dr. Fuller claims was his way of indicating an animal's participation in the study, Dr. Fuller admitted placing these entries in the medical records after FDA investigator Lochner had begun his inspection. This admission followed Dr. Fuller's earlier denials to Mr. Lochner that the medical records had been tampered with during the inspection.

I will discuss these findings in greater detail below.

A. Affidavits from Animal Owners

The protocol for the Study" states that:

> **Doges of various breeds, ages, and sex exhibiting pain and/or inflammation referable to disorders in one or more of the following musculoskeletal categories are candidates for evaluation:**
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> - **o Acute Intervertebral Disc Syndrome**
> - **o Acute Hip Dysplasia**
> - **o Surgical Cases**
> - **o Traumatic Injuries**

Exhibit 1, p. 2.

Dr. Fuller submitted 43 case report forms to Exhibits 3-45. An overwhelming number of the reports - 39 of the 43 cases - were classified as traumatic

injuries.[2] See exhibits 4, 7-18, 20-45. The source of trauma was identified in 31 of the 39 cases. Five dogs supposedly injured themselves jumping from furniture. Exhibits 9, 23, 27, 31, 41. Seven dogs were reported as jumping from cars or trucks. Exhibits 8, 11, 16, 32, 35, 37, 42. Eight dogs were reported as receiving injuries from doors. Exhibits 10, 13, 14, 15, 21, 24, 28, 36. Two dogs had chairs listed as the source of trauma. Exhibits 17, 38. Four dogs supposedly injured themselves jumping off or falling from porches or steps. Exhibits 30, 33, 34, 45. Another four dogs were said to have tripped. Exhibits 12, 39, 43, 44. One dog was supposedly kicked by a cow.[3] Exhibit 40.

Dr. Dobozy, the FDA veterinary medicine officer who reviewed Dr. Fuller's study, testified that Dr. Fuller's ability to determine the source of trauma for such a large percentage of animals (79.5%) aroused her suspicions. Transcript at 22, 24-25. Dr. Dobozy testified that it is unusual for so many pet owners to be aware of the source of trauma to their pets. Therefore, she requested an agency

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[2] The remaining four cases were classified as follows: one surgical (exhibit 19), one "disc" (exhibit 5), and two "miscellaneous" (exhibits 3, 6).

[3] The remaining eight reports do not identify the source of trauma.

investigation to determine whether the information in Dr. Fuller's case reports was correct. Transcript at 19-23.

Obviously, one way to confirm whether the information in the case reports is correct is to ask the animal owners to verify the source of trauma supposedly suffered by their dogs. FDA investigator Lochner attempted such verification by interviewing the owners whose animals - presumably dogs -were supposedly enrolled in the study. Mr. Lochner was able to interview 22 of the 40 owners. Transcript at 42. A significant number of the animal owners - 14 out of 22 -denied that, or could not remember whether, their animals were either injured or treated in the manner described in the case report forms. Transcript at 50. For example, exhibit 7 is a case report for a 40-lb. mixed breed dog named owned by Mr. The case report contains a diagnosis of "severe limp of the left front paw [unintelligible] traumatic injury cause not known." In contrast, Ms. affidavit, exhibit 86, clearly states that, "We have a pet named It is a cat, not a dog. It is a domestic long hair and weighs about 14 pounds (not 40 pounds)." Ms. also wrote that "He did not develope [sic] a severe limp of the left front paw that needed treatment by Dr. Fuller in March 1985."

Similarly, exhibits 14 and 40 are case reports for a mixed breed dog, and a collie named The owner listed on both reports is The case report's diagnosis for is "severe bruising over dorsal spine in lumbar area...garage door closed on him. No apparent fracture." For the case report notes that the animal "was kicked by a cow in the left lumbar area." An affidavit executed by Ms. (exhibit 89) states that:

> Neither dog was injured last Spring and had to be treated by Dr. Fuller at the Animal Hospital with tablets. was not caught in a garage door bruising his lumbar area in April 1985. was not kicked by a cow in the left lumbar area. We stopped taking our dogs to Dr. Fuller more than a year ago. They were not to him in 1985.

Several other owners wrote similar denials of injuries and treatment to their pets. The case report for a Cairn Terrier named owned by Ms. states that the dog was "Caught in screen door...." Exhibit 15. Ms. affidavit confirms that she owns a Cairn Terrier named . However, Ms. affidavit also declares that:

> was not injured last April needing treatment by Dr. Fuller at the Animal Hospital. He was not caught in a screen door bruising his left lumbar area. He was not treated with tablets. I called my husband about this. He also does not remember such an injury or treatment.

Exhibit 90. Mrs. denied that she or her husband found their dog, a Schnauzer named limping one day, or that the dog was treated with as reported on the case report for See exhibits 20, 91. Similarly, Ms. denied that her dog a Pomeranian, was injured jumping off a couch or even treated with as reported on the case report form. See exhibits 27, 95. Other owners executed similar affidavits. See, e.g., exhibits 92, 94, 96, 97, 98, 101, 102. See also Transcript at 43-50.

Collectively and individually, these affidavits directly challenge the validity of the case reports. Although some affiants did state that they "could not remember,"[4] the fact that many other owners wrote that the injury or treatment did not happen is extremely troubling. It is difficult to conceive of a situation where a veterinarian would know the source of trauma to a dog while the dog's owner would not, especially where the animal supposedly received its injuries

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[4] I have elected to disregard the statements made in the affidavits from owners who wrote that they could not remember or refused to sign the affidavit. Although Mr. Lochner testified that he believed that several owners who said they could not remember if their animals were injured or treated were nevertheless "very certain" that the case reports's information was untrue, I cannot favor Mr. Lochner's perceptions over the written statements in the affidavits.

in an atypical fashion as in the cases where one dog was supposedly caught under a garage door and the other kicked by a cow. Nevertheless, the case reports purport to do this for a number of animals and have even declared a cat, to be a dog. See exhibits 7, 86. The frequency of injuries is also striking. Dr. Dobozy testified that Dr. Fuller's cases showed 39 traumatic injuries within a three month period whereas the next largest number of traumatic injuries in an investigator's case reports was 17 within a five month period. Transcript at 25. The owners's affidavits do not suggest that traumatic injuries are common to dogs in the Newark area. Indeed, many affiants said their pets were not injured during the time listed in the case report forms.

At the very least, these facts make one suspect the validity of the case report forms. Consequently, if the information in the case reports is to be verified at all, such verification must come from other sources, and so I will now discuss the only other objective source for support: the medical records.

B. The Medical Records

Medical records serve two purposes in a clinical investigation. First, the records provide the animal's

medical history to the investigator thereby serving as a valuable source of information. Second, medical records are a means of supporting the information reported in case report forms. This second function becomes critical when the entries in the case reports are under question.

In this case, only two medical records appear to support that the animal in question actually participated in the study. The medical records for the animals named (exhibit 46) and (exhibit 47) clearly state that received and was given "Experimental A."[5] The case reports for these animals, however, contain different information. case report, as Mr. Lochner testified, shows that the dog received "drug A" which was the placebo in the study. See exhibit 3; transcript at 36-37, 40-41. case report shows that the dog received "drug B" - instead of "Experimental A." See Exhibit 4. Therefore, even the medical records that confirm participation in the study fail to confirm the information in the case reports.

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[5] I also note that the medical record for indicates that the dog received in an injectable form whereas the in the clinical study was only in tablet form. However, because the propriety of the injectable dosage form's use in dogs is not at issue in this hearing, I will not discuss it further.

Although Dr. Fuller did not appear at the hearing or present any evidence or documentation on this or any other issue in this proceeding, I note that in his affidavit (exhibit 103), Dr. Fuller claimed that he recorded information directly into the case report forms rather than into the medical records. Such a practice is not improper per se, but it does leave the record devoid of any support for the case reports.

Moreover, Dr. Fuller's explanation is not consistent with other actions that he took. Two medical records indicate that a dog was treated with or was in the study. Although these records conflict with the case reports, they clearly show that, contrary to the assertions in his affidavit, Dr. Fuller did make entries in the medical records at least for these two animals.

The administrative record also shows that Dr. Fuller attempted to make the other medical records support the case reports after Mr. Lochner began his inspection at the Animal Hospital. Specifically, Dr. Fuller wrote ' on the medical records sometime between the first and second day of the inspection. According to Mr. Lochner, Dr. Fuller said that ' stood for and initially told Mr. Lochner that the notation had always been in the medical

records. Transcript at 39. Dr. Fuller's own affidavit confirms this account.[6] See exhibit 103.

Yet instead of supporting the case reports as Dr. Fuller intended, the entries only cast more doubt as to the validity of the case reports. Many notations in the medical records are out of chronological order and appear to have been put in blank spaces between entries. For example:

- the dog named or supposedly participated in the trial between March 7-9, 1985. Exhibit 6. The dog's medical record has the ' notation in an entry for March 6, 1985. Exhibit 49.
- the animal named : supposedly participated in the . trial between March 14-16, 1985 (exhibit 8), yet its medical record has the entry on March

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[6] In his affidavit, Dr. Fuller states that he did not make the entries in an attempt to deceive Mr. Lochner. I cannot entertain such a statement. Mr. Lochner's testimony, as well as Dr. Fuller's affidavit, shows that Dr. Fuller initially told Mr. Lochner that the entries had always been on the records, but that Mr. Lochner must have "overlooked" them. See Transcript, pp. 39-40; exhibit 103. Dr. Fuller later retracted this statement and admitted making the entries after Mr. Lochner had begun his inspection. The alteration of medical records during an FDA inspection, coupled with Dr. Fuller's effort to mislead Mr. Lochner, could have no other purpose than to deceive an FDA investigator in the course of his duties.

4, 1985. Cf. exhibit 50. Additionally, the notation is in the middle of an otherwise blank line in the medical record.

- The case report for shows participation in the study from April 4-5, 1985. Exhibit 18. In contrast, the medical record entry for April 4, 1985 does not show any drug administration or traumatic injury, and the entry is followed by a notation dated April 3, 1985. Exhibit 61. The notation also occupies the only space between the entries for April 4, 1985 and April 29, 1985. In contrast, the other entries in the medical record have blank spaces between them. Id.

- a Labrador owned by Mr. supposedly caught his right front paw under a garage door and received on May 1-2, 1985. Exhibit 36. The case report states that the injury was "Very painful, but no apparent fracture on palpitation." Id. Alexander's medical record bears the notation on the entry

> for May 1, 1985, yet four lines above the notation, for the same date, the medical record reports "No problems." Exhibit 77. If suffered a severe injury, as claimed in the case report, the injury cannot be reconciled with the "No problems" entry for the same time period.
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> subsequent medical history also raises some questions. The medical record's entry for May 15, 1985 reads that took off. Hasn't come home...Doing very well. Mrs. thinks has a 'girlfriend' in the neighborhood." Id. Such behavior seems quite inconsistent for a dog who, according to the case report form, supposedly suffered a "very severe injury" less than two weeks earlier. See exhibit 36.

In summary, therefore, the medical records fail to provide any reason to believe in the validity of the case reports. The medical records conflict with the information in the case reports, contain entries that were admittedly entered after Mr. Lochner began his inspection, and fail to support the dates and diagnoses in the case reports.

C. Non-Listing of Concomitant Drug Use in Case Reports

Aside from the problems with the diagnosis and dates in the case report forms, the case report form for the study also contained a section asking for the animal's history, including "concomitant disorders and therapy for unrelated disorders." See, e.g., exhibit 3 (emphasis added). Here, a substantial number of case reports do not show concomitant therapy as indicated in the medical records. The medical records show that the dogs were given various drugs in tablet and injectable forms, yet the case reports are uniformly silent as to any other therapy. See, e.g. exhibits 6, 9, 12, 13, 16, 49, 52, 55, 56, 59. Thus, again, the case reports are not supported by the medical records.

Conclusion and Recommendation

This regulatory hearing has been held to determine whether Dr. Fuller repeatedly or deliberately submitted false information in the case report forms in violation of 21 CFR 511. After reviewing the evidence and hearing the testimony, I conclude that Dr. Fuller did submit false information in the case report forms. To briefly recapitulate my findings, neither the affidavits of the owners of the animals supposedly

enrolled in the study nor the medical records for the animals support the information in the case reports. A significant number of owners submitted affidavits that declared that their animals were not injured or treated in the manner described in the reports. The high frequency of traumatic injuries relative to the reports from other investigators raises questions as well. Medical records for the animals are either inconsistent with the case reports or fail to support the case reports altogether.

Therefore, on the basis of the testimony, the absence of any assurance from Dr. Fuller that FDA regulations will not be violated in the future, and the administrative record, I find that Dr. Fuller has violated of 21 CFR 511.1 by repeatedly submitting false reports to the sponsor of the Banamine investigation. I recommend that Dr. Fuller be declared ineligible to receive investigational new animal drugs.

Stuart L. Nightingale, M.D.
Presiding Officer and
Associate Commissioner
for Health Affairs

cc: R.R. Fuller
M.S. Drozen