



United States
General Accounting Office
Washington, D.C. 20548

10461910

Office of the General Counsel

~~NOT BE AVAILABLE TO PUBLIC READ~~
FOR 30 DAYS

B-257122

October 19, 1994

The Honorable George E. Brown, Jr.
Chairman, Committee on Science, Space
and Technology
House of Representatives

The Honorable David Obey
House of Representatives

The Honorable Bernard Sanders
House of Representatives

 This is in response to your letter dated April 15, 1994. You asked us to examine alleged conflicts of interest on the part of three Food and Drug Administration employees in the approval of Monsanto's Posilac and the related issuance of voluntary milk labeling guidance. You also asked that we determine whether any FDA employees involved in the approval of Posilac had an appearance of the loss of impartiality because of a prior relationship with Monsanto.

^ To conduct our investigation, we reviewed more than 40,000 pages of documents; conducted 54 interviews with current and former FDA and Department of Health and Human Services employees, attorneys, Monsanto officials, and editors of scientific journals; reviewed the financial disclosure and conflict-of-interest statements of all Center for Veterinary Medicine employees who played a significant role in Posilac's approval, and reviewed the relevant ethical standards.

On the basis of our review of the law, examination of documents and interviews, we conclude that there were no conflicting financial interests with respect to the drug's approval or the voluntary milk labeling guidance. With respect to the approval of Posilac, we noted only one minor deviation from now-superseded FDA regulations. Finally, with respect to Monsanto's application for Posilac, we identified several

561431 / 152883

articles whose publication may have been contrary to FDA's requirements for prior approval of outside activities.

We have enclosed our more detailed analysis of the allegations concerning the three individuals. Unless you release it sooner, this letter will be available to the public 30 days from its date.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Robert P. Murphy".

Robert P. Murphy
Acting General Counsel

Enclosure

ENCLOSURE

SUMMARY OF RESULTS

At the request of three Members of Congress, we have reviewed the alleged conflicts of interest of three Food and Drug Administration (FDA) employees in (1) the FDA's review and approval of the Monsanto Agricultural Company's New Animal Drug Application (NADA) for Posilac¹ and (2) the promulgation of interim labeling guidance for milk produced from other than rbst² treated cows. The review covers the FDA activities of Dr. Margaret Miller and Mr. Michael Taylor who, prior to coming to work for FDA, were, respectively, employed by and an attorney for Monsanto. The report also covers the activities of Dr. Suzanne Sechen who came to FDA after completing graduate school.

On the basis of our review of the law, examination of documents and interviews, we conclude that neither Drs. Miller or Sechen nor Mr. Taylor had conflicting financial interests with respect to the approval of Posilac or the promulgation of the interim milk labeling guidance. We also conclude that there were no transgressions of the Office of Government Ethics (OGE) Standards which currently govern the appearance of the loss of impartiality. While we identified one minor deviation from FDA's now-superseded appearance standards, we do not believe that it affected the decision to approve sometribove. However, we identified several articles whose publication may have been contrary to FDA's requirements for prior approval of outside activities. Although we did not find that publication of these articles affected approval of Monsanto's NADA, FDA needs to take steps to inform employees of their responsibilities to get approval of outside activities.

To perform our review, we examined federal conflict of interest statutes and the ethics standards that govern the duties of executive branch employees. In addition to the Center for Veterinary Medicine (CVM), we gathered information from the FDA's headquarters and its Center for Food Safety and Applied Nutrition (CFSAN), OGE, the Department of Health and Human Services (HHS), Mr. Taylor's former law firm of King

¹ Posilac is Monsanto's trademark name for the compound sometribove, a bovine somatotropin produced with recombinant technology. Sometribove has been found by FDA to increase milk production in healthy lactating dairy cows. Throughout the report Posilac and sometribove will be used interchangeably.

² Recombinant bovine somatotropin.

ENCLOSURE

& Spalding, current and former FDA employees, Monsanto employees and ethics professionals.

We examined more than 250 of the volumes comprising Monsanto's new animal drug application, proceedings of Advisory Committee meetings, billing statements, financial disclosure statements, official personnel folders, and personal documents from CVM and CFSAN officials that we interviewed. These personal documents included electronic files, personal calendars, drafts and memoranda, personal notes, and scientific literature. We reviewed the guidance on voluntary milk labeling, and HHS, FDA and OGE regulations concerning ethics and ethics training, and other ethics provisions.

We interviewed Mr. Taylor and Drs. Miller and Sechen. We also met or talked with 51 current and former FDA officials, as well as former associates of Mr. Taylor and of Drs. Miller and Sechen, and Monsanto employees. We discussed the approval process for new animal drug applications, issues related to sometribove's approval, and the role of Drs. Miller and Sechen, and Mr. Taylor. A complete list of the people with whom we spoke is included in Appendix I to this opinion. We obtained informal comments from FDA on a draft of this report.

CRITERIA

There are two issues raised by the conflict of interest questions we were asked. The first concerns whether an employee has a conflicting financial interest in the outcome of a particular matter. By statute³ and

³ Conflicting financial interests are prohibited by 18 U.S.C. § 208 which states in relevant part,

"[W]hoever, being an officer or employee of the executive branch of the United States Government . . . participates personally and substantially as a Government officer or employee, through decision approval, disapproval, recommendation, the rendering of advice, investigation, or otherwise in a judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, arrest, or other particular matter in which to his knowledge, he, his spouse, minor child, general partner, organization in which he is serving as an officer, director, trustee, general partner or employee . . . has a financial interest--

Shall be subject to the penalties set forth in 216 of this title."

ENCLOSURE

regulation employees are generally prohibited from participating in particular matters affecting companies in which they have a financial interest.

The second concerns whether, although the employee may have no financial interest in the outcome of a particular matter, the employee's involvement in that matter would cause a reasonable person in possession of the relevant facts to question the employee's impartiality.⁴ Determining whether there is an appearance of the loss of impartiality requires an examination of, among other things, the relationship between prior business associations and current decision making.⁵

The second issue was governed by HHS/FDA Standards of Conduct⁶ from the time Monsanto submitted its new animal drug application until February 3, 1993. On that date, OGE's Standards of Ethical Conduct for Employees of the Executive Branch⁷ became effective superseding the old HHS/FDA regulations; subsequent conduct is subject to the OGE regulations.

Although both the FDA and OGE standards contain provisions to assist employees avoid appearance problems, the provisions differ in their application. The FDA standards permanently prohibited employees from working on the same regulatory matter⁸ in which they had participated

⁴ 5 C.F.R. Part 2635 Subpart E (1994).

⁵ The Office of Government Ethics provides, as an example, the case of an electronics company vice-president who has just resigned her position to accept a job at the Federal Aviation Administration. OGE states that the employee would be correct in concluding that her former service as an officer of the company would be likely to cause a reasonable person to question her impartiality if she were to participate in the administration of a FAA contract with her previous employer.

⁶ 45 C.F.R. Parts 73 and 73a (superseded, in part, February 3, 1993).

⁷ 5 C.F.R. Part 2635 (1994).

⁸ FDA regulations used the phrase "regulatory matter," which has been defined by the agency to mean a specific regulatory action such as the approval of one company's new animal drug. It does not encompass policy statements or decisions applicable to many companies or persons. This definition is consonant with OGE's definition of a "particular matter involving specific parties." Opinion of HHS Designated Agency Ethics Official dated March 11, 1994, pg. 4, fn. 3; see, 5 C.F.R. § 2637.201(c) (1994).

ENCLOSURE

personally and substantially on behalf of their former employer.⁹ Further, employees could not work on other regulatory matters related to their former employer for one year after joining the government.¹⁰

The OGE impartiality standards replaced prior appearance standards as applied to impartiality issues. The new standards provide employees with a procedure to avoid an appearance of the loss of impartiality in the performance of their official duties. Where an employee knows that a person with whom he has a "covered relationship"¹¹ is or represents a party in a particular matter involving specific parties,¹² and where the employee determines that the circumstances would cause a reasonable person with knowledge of the relevant facts to question his impartiality in the matter, the employee should not participate in the matter, unless authorized.

In addition, the standards provide that employees, who believe

⁹ The regulation, 45 C.F.R. § 73a.735-201(b) (1993), stated,

"A control activity employee who was previously employed in a regulated organization shall not participate in any regulatory action before FDA in which the employee had participated personally and substantially on behalf of the former employer organization, e.g., drug investigations/applications, food additive petitions, matters dealing with compliance in areas of radiation-producing products or medical devices. Exceptions may be authorized only under paragraph (e) of this section."

¹⁰ In relevant part, FDA's regulation stated that,

"For a period of 1 year after FDA appointment, or appointment to the Food and Drug Division, Office of the General Counsel, a control activity employee who was employed in a regulated organization within 1 year before FDA employment shall not participate in any regulatory action before FDA that involves the former employer organization." 45 C.F.R. § 73a.735-201(a) (1993).

¹¹ Covered relationships include, among other things, "Any person for whom the employee has, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee." 5 C.F.R. § 2635.502 (b)(1)(iv) (1994). (emphasis added)

¹² These generally involve a specific proceeding affecting the legal rights of a specific party or parties. This is to be distinguished from rulemaking, and policy or standard formulation that typically apply to broader categories of parties. See generally, 5 C.F.R. §§ 2637.102(a)(7) and 2637.201(c) (1994).

ENCLOSURE

circumstances, other than those specifically described, would raise a question regarding their impartiality, should consider whether a reasonable person with knowledge of the relevant facts would question their impartiality in the matter. To make this determination, employees may consult with agency officials.¹³

The context in which individual actions occur is critical to understanding their legal significance. In order to provide the context for Monsanto's NADA what follows is a brief description of the NADA process.

SOMETRIBOVE REVIEW PROCEDURE AND APPROVAL DATES

A person who wishes to sell a new animal drug must first obtain approval from the FDA. In order to obtain approval the person, known as a sponsor, must prove that the product is safe and effective when used as directed.

The process may start with an Investigational New Animal Drug application (INAD). An INAD permits the interstate shipment of unapproved drugs for investigational use. This, according to FDA, allows a drug sponsor to obtain safety and efficacy data to support the filing of a NADA.

Once a NADA is received, it is assigned to a primary review division within CVM. A primary reviewer in that division is then responsible for ensuring that all sponsor submissions are reviewed by the appropriate technical divisions of CVM. These submissions are made up of pivotal scientific studies that FDA evaluates for human health safety, drug effectiveness, target animal safety,¹⁴ environmental impacts and

¹³ 5 C.F.R. § 2635.502(a)(2) (1994) states

"An employee who is concerned that circumstances other than those specifically described in this section would raise a question regarding his impartiality should use the process described in this section to determine whether he should or should not participate in a particular matter."

¹⁴ Target animal safety studies examine the toxicological effects of different drug dosages (e.g., 1x, 2x and 3x) on the animal to which the drug would be administered if approved.

ENCLOSURE

manufacturing practices. The sponsor also submits non-pivotal studies to provide additional information. Non-pivotal studies are not key elements of the approval process, and are examined mostly for gross inconsistencies with pivotal study data.

Technical reviewers evaluate a sponsor's submissions for accuracy, completeness and validity. After data analysis and methodological review the technical reviewers prepare a statement of recommendations and comments, noting deficiencies in each submission. Each reviewer's statement is reviewed by his/her branch chief and division director before being sent back to the primary reviewer.

The primary reviewer will check the technical reviewer's statement for validity and accuracy. These findings are incorporated into a transmittal letter which is reviewed by the primary reviewer's branch chief and division director before being sent back to the sponsor for further action. The sponsor's studies, and FDA's reviews, are placed into files maintained by FDA. These files comprise the NADA.

Monsanto filed an INAD for recombinant bovine growth hormone in May, 1981. It submitted its NADA¹⁵ for sometribove in 1987. The human health safety study was completed on August 28, 1989. The effectiveness and target animal assessments were completed on March 30, 1993. The environmental and manufacturing reviews were completed on May 7, 1993. Sometribove was approved by FDA on November 5, 1993. In a related and separate action, FDA published interim milk labeling guidance on February 10, 1994.

THE NEW ANIMAL DRUG APPLICATION

You have asked us whether, in light of Dr. Miller's, Dr. Sechen's, or Mr. Taylor's prior associations with Monsanto, their activities at FDA with respect to the NADA created the appearance of a loss of impartiality. As stated above, there are two issues of concern raised by your questions: whether the individuals had conflicting financial interests and whether they violated applicable standards governing appearance of a loss of impartiality.

¹⁵ At the time that Monsanto submitted its application for sometribove, three other drug companies were investigating different rbST formulations.

ENCLOSURE

CONFLICTING FINANCIAL INTERESTS

We did not find a conflicting financial interest for any of these employees. Our determination is based on our review of their certified financial disclosure and conflict of interest statements.

Dr. Miller severed all financial ties with Monsanto upon joining FDA and has not since established any new financial interest. Therefore, we found she did not have a financial conflict.

Dr. Sechen never worked for Monsanto and never had any financial ties with Monsanto to sever. She has not, since working at FDA, established a financial interest in any company regulated by the agency. Therefore, we found that she did not have a conflicting financial interest.

Mr. Taylor, previously an attorney for Monsanto, did not participate in FDA's decision to approve Posilac either directly or indirectly. Since he would have had to have participated to create a conflict, it is impossible, by definition, for him to have had a financial conflict of interest.¹⁶

The remainder of this report is divided into (1) sections analyzing separately Dr. Margaret Miller's, Dr. Suzanne Sechen's and Michael Taylor's role in the NADA approval process in light of criteria governing appearances of a loss of impartiality and (2) a section analyzing Michael Taylor's role in promulgation of the interim milk labeling guidance.

APPEARANCE OF THE LOSS OF IMPARTIALITY

Dr. Margaret Miller

Activities prior to February 1993

From 1985 until her employment by FDA in December of 1989, Dr. Miller worked for the Monsanto Company as a chemical laboratory supervisor. In that position she was responsible for validating tests which measured levels of (1) bST in cow blood, tissue and urine and (2) insulin-like growth factor-I in cow liver and muscle. She also attempted

¹⁶ See footnote 36 for a discussion of the waiver granted to Mr. Taylor for financial interests imputed to him.

ENCLOSURE

to verify the measurement of bST in milk.¹⁷ Finally, she performed all the analytical work to support the target animal safety studies for sometribove.

Dr. Miller began work at FDA on December 3, 1989. She was counseled at the time of her employment by FDA on existing agency ethics standards. These standards required her recusal from all Monsanto-related activity for one year as well as a lifetime ban on regulatory actions with which she had been personally and substantially involved at Monsanto (see footnotes 9 and 10).

Dr. Miller started her career at FDA as a reviewer in the Antimicrobials and Antiparasitic Branch of the Division of Toxicology and Environmental Sciences, where she evaluated antimicrobial and antiparasitic drugs. In late December of 1990 or early January 1991, she helped draft FDA's answer to a citizen's petition seeking, in part, to halt all sales of milk from cows treated with rbST. Dr. Miller worked as a reviewer until February 1991, when she became Acting Branch Chief.

From August to November 1991, she was Director of the Division of Toxicology and Environmental Sciences, a position that was directly involved in the technical review of sometribove. She took steps to avoid reviewing any material related to Monsanto's application. These actions included: (1) informing her supervisors that she could not work on the Monsanto NADA and (2) not reviewing documents that were related to the application. We were able to confirm that she had made it known to people with whom she worked that they should not provide her with material related to the sometribove application.

From November 1991 until February of 1992, Dr. Miller returned to reviewing drug applications in the Antimicrobial and Antiparasitic Drugs Branch. In February of 1992 she became Branch Chief for Hormones and Pharmacological Agents in the Division of Toxicology and Environmental Sciences. This branch had been responsible for

¹⁷ Apparently, an assay purporting to measure bST in milk had been described in an article submitted for publication by another Monsanto scientist. The article was rejected because the assay was not sensitive enough to measure bST in milk. Dr. Miller, as an assay expert, was given the task of either fixing the assay that had been submitted or developing a new test to measure bST in milk. As a result of her attempts to either fix or replace the assay, she concluded that it was not possible to measure the bST directly with current immuno assay techniques.

ENCLOSURE

reviewing the human safety aspects of Monsanto's NADA. As branch chief, she would draft responses to congressional correspondence that related to rbST. It was her policy and practice to refer matters relating to sometribove's approval to the Division Director for his signature.

As Branch Chief, in August 1992, she concurred in the wording of a freedom of information summary relating to Posilac's human health safety aspects. A freedom of information summary is usually prepared by the sponsor and reviewed by CVM after it has reached a decision on a particular aspect of the NADA, in this case, human health safety. The statement is intended to capture the information underlying that decision in a document that can be distributed to the public without releasing the sponsor's proprietary information.

From November of 1992 until February of 1993, she worked at home as a reviewer. In this capacity she helped draft an answer to a letter from Senator Kohl, dated October 30, 1992. Senator Kohl's letter included a critique of the science behind FDA's sometribove approval process and raised questions regarding the adequacy of FDA's data and studies. Between 1990 and 1993, Dr. Miller was co-author of several articles in scientific journals. These articles were based on her work at Monsanto, and will be discussed separately later.

Analysis of Dr. Miller's Activities before February 1993

Between December 1989 and February 1993, Dr. Miller was permanently prohibited from participating in those regulatory matters with which she had had substantial personal involvement at Monsanto. Since her employment at Monsanto consisted in large part of work on sometribove, at a minimum she would have been prohibited from working on the review of those parts of the NADA¹⁸ that were related to her prior work. She was also not to work on any issue related to Monsanto for the first year of her employment. In this connection she engaged in activities during this period of time which warrant discussion.

First, she drafted an answer to a citizen's petition dated December 4,

¹⁸ We accept FDA's own conclusion that Monsanto's NADA constituted a regulatory matter within the meaning of FDA regulations.

ENCLOSURE

1990.¹⁹ In relevant part, the petition sought to remove from sale all milk produced with rbST products. The question with respect to Dr. Miller's involvement is (1) whether the petition constituted a regulatory matter and if so, (2) whether it is the same matter from which she had been recused.

A regulatory matter, as set forth in FDA's standards, typically involves a specific proceeding affecting the legal rights of a specific party or parties. This is to be distinguished from rulemaking, and policy or standard formulation that typically apply to broader categories of parties.

In this case, the petitioner argued in general terms that the safety of all milk from rbST-treated animals was suspect due to the presence of insulin-like-growth factor-I. Although approval to sell products from animals treated with an investigational drug is dependent on each drug's composition, the petition did not challenge the composition or method of action of any of the various rbST products then under investigation. Therefore, FDA was not called upon to and did not decide on the safety of specific rbST formulations but rather looked at general principles applicable to all rbST. FDA, interpreting its own regulations, stated it was not likely that this would have been considered a regulatory action.²⁰

However, even assuming that the answer to this petition constituted a regulatory action, we do not believe that there would have been a bar to Miller's involvement because it would not have been the same action as the review of Monsanto's application for sometribove. Further, the petition did not directly address the merits of that application.

Second, in August of 1992, Dr. Miller, in her capacity as Branch Chief for Hormones and Pharmacological Agents in the Division of Toxicology and Environmental Sciences, concurred in the freedom of information summary for human safety that became part of the NADA files. Freedom of information summaries are prepared after a decision has already been made by CVM on some particular aspect of the NADA and their purpose

¹⁹ This petition was dated one year and one day after Dr. Miller began working at FDA and therefore her work occurred outside the one year general recusal from all Monsanto-related regulatory issues.

²⁰ Memorandum to the Record from Jane E. Henney and Margaret Jane Porter, November 4, 1993, fn. 1.

ENCLOSURE

is to commit to paper the basis for the decision.²¹ As noted earlier, the human health safety study was completed on August 28, 1989, while Dr. Miller was still a Monsanto employee. Dr. Miller's signature on this document constitutes participation in the NADA review process and therefore is a technical violation of FDA regulations in effect at that time. We believe that her concurrence in the summary of a previous determination on human safety issues was a minor matter that did not have an effect on the approval of Posilac from the standpoint of human safety issues.

Activities after February 1993

Dr. Miller returned to work at CVM in February of 1993, resuming her position as Branch Chief for Hormones and Pharmacological Agents in the Division of Toxicology and Environmental Sciences. In 1993, the Office of Government Ethics Standards removed FDA's lifetime ban on her involvement with the approval of sometribove. Since Dr. Miller had been an FDA employee for over three years, OGE's standard on appearance of loss of impartiality was not applicable. After February 1993, Dr. Miller became more involved in the issues surrounding approval of sometribove. Her involvement came not because of the ban's removal,²² but rather as a result of Commissioner Kessler's concerns about human health safety. Current and former senior CVM officials told us that Dr. Miller had consistently brought to their attention her concern about staying within the spirit and letter of the ethics restrictions.

In August of 1992, GAO reported²³ that rbST causes higher rates of

²¹ Additionally, there is some evidence that a concurrence from Dr. Miller's Branch on this particular document was superfluous to its inclusion in the NADA.

²² Dr. Miller's supervisors at the time were unaware that there was such a ban, much less that it had been removed.

²³ Recombinant Bovine Growth Hormone, FDA Approval Should be Withheld Until the Mastitis Issue is Resolved, GAO/PEMD-92-26; B-248450, August 6, 1992. See also, March 2, 1993 letter from Eleanor Chelimsky, Assistant Comptroller General to Donna E. Shalala, Secretary of Health and Human Services, B-248450. In this document GAO stated, "It is unclear how FDA can make a serious determination of the rBGH-mastitis-antibiotic issue without revisiting the human food safety review." pg. 3.

ENCLOSURE

mastitis²⁴ in cows which in turn could lead to higher levels of antibiotics in milk. Because the standard treatment for mastitis includes giving the cows antibiotics, GAO reasoned that increased mastitis could lead farmers to use greater amounts of antibiotics to treat the condition. The study concluded that the potential for increased use of antibiotics could increase the amount of drug residue in milk and called on FDA to study the potential risk posed by a possible increase in drug residue in milk before approving the drug. In mid-January 1993, the FDA Commissioner requested that FDA convene two advisory committee meetings. The first meeting, held in March, was to discuss issues related to the GAO report and the second meeting, held in May, was to deal with milk labeling.

On March 10, 1993, FDA announced that it would hold a meeting of its Veterinary Medicine Advisory Committee (VMAC) at the end of the month to discuss whether approval of sometribove would lead to increased human health risks. At the same time the agency announced that CVM had reached the tentative conclusion that use of sometribove would not lead to an increased risk to humans. Dr. Miller attended the meeting but did not participate.

In early April, 1993, Dr. Gerald Guest, then the Director of CVM, asked Dr. Miller²⁵ to provide him with a paper discussing whether or not it was possible to distinguish between bST and rbST in milk using current assay technology. At the time he asked her, Dr. Miller told him that she had worked for Monsanto on the question of measurement and that in her opinion it was not possible to measure bST in milk much less differentiate between endogenous and recombinant growth hormone. She was concerned that her involvement might create a problem, first because her past work, contrary to published literature, indicated that it was not possible to measure bST in milk and second because her prior work had been done for Monsanto. Dr. Guest said that he wanted her professional opinion and told her to undertake the work. Later, at Deputy Director Dr. Richard Teske's request, she prepared a shortened version of the paper which was to be used in briefing Commissioner Kessler.

²⁴ An infection of cow udders.

²⁵ Because Dr. Miller was in charge of developing CVM policy on antibiotic residue in food it was logical that senior agency officials would seek her participation in answering the concerns posed by GAO.

ENCLOSURE

Dr. Miller later attended the May 1993 joint meeting of the VMAC and Food Advisory Committees where the issue of labeling milk produced by cows injected with rbST was discussed. In an earlier planning session involving CVM officials, it was suggested that Dr. Miller make a presentation to the joint meeting on behalf of CVM. We were told that the suggestion was quickly dismissed because the Center Director (Dr. Guest) thought it would have created an appearance problem.²⁶

In May 1993, Dr. Miller believes that she was approached by either the Director of the Division of Biometrics and Production Drugs, Dr. Richard Lehmann, or Dr. Teske, who asked her whether she could answer basic bovine endocrinology questions about bST for Commissioner Kessler. She said she could. On May 20, 1993, Dr. Sechen, the primary reviewer for rbST products; an attorney from FDA's Office of Chief Counsel; an endocrinologist from the Center for Drug Evaluation and Research; and Dr. Miller briefed the Commissioner on issues related to bST. He had a number of scientific questions about the action of growth hormone in cows and how that differed from the action of growth hormone in humans. Dr. Miller and the others answered the Commissioner's questions, some of which were related to bST and others were specific to sometribove.

Dr. Miller told us that on June 10, while attending a conference on endocrinology, she received a call from then-Acting Center Director Teske asking her to prepare a note on whether the increase in mastitis associated with the use of rbST is directly attributable to the rbST. He told her that the Commissioner had expected an answer from her earlier. Dr. Miller told us that she did not recall being asked about mastitis by the Commissioner and she was puzzled by the request because she was not an expert in the area. The information provided by Dr. Miller was included in a note to Commissioner Kessler dated "6/10/93" and was part of a briefing packet for a meeting on sometribove with the Commissioner on June 21, 1993.

²⁶ We were told by Center officials that they limited attendance at the VMAC meeting to those involved in the sometribove approval process due to lack of space. A list of those who were to attend was prepared and everyone else was discouraged from attending. Dr. Miller may have sought and gained permission to attend. She told us that she was interested in greater management responsibilities at the Center and attending the committee meeting was one way to demonstrate her interest in advancing.

ENCLOSURE

During the summer of 1993, FDA was also evaluating whether it should require Monsanto to conduct a post-approval study as a condition to approving Posilac.²⁷ At the time, because it appeared that the study would involve human food safety concerns, senior Center officials asked Dr. Miller to get involved in helping develop the protocol. She sat in on one telephone conversation. During the course of the conversation, she discovered that (a) the study would deal with target animal safety and (b) it would involve the people she had worked with at Monsanto. She left the room and did not take part in any further discussions related to the study. Dr. Miller later explained to Center officials that she felt it would be inappropriate to be included in further discussions because she would be put in the position of having to negotiate with her former Monsanto colleagues. Ultimately Monsanto agreed to conduct the study, and while this agreement was not part of the formal approval, in words of one FDA official, it was clear that the post-approval study and approval of sometribove were part of a package deal.

On June 25, 1993, the Director of the Division of Biometrics and Production Drugs sent a letter to Monsanto stating, "This submission completes your firm's new animal drug application for Posilac. We have no further outstanding issues for which your firm needs to provide additional submission to this NADA." The Commissioner was concerned this letter might incorrectly signal Monsanto that FDA officials believed the drug to be approvable. He contacted the head of CVM and directed him to send a letter that was reflective of the agency's overall position. This second letter, sent on July 6, 1993, states, "In particular the Agency continues to deliberate the significance of the increases in mastitis among cattle supplemented with Posilac and significance of any resultant increase in the use of antibiotics."

In 1993, Dr. Robert Condon, Senior Regulatory Review Scientist and Mathematical Statistician, analyzed the increased risk of antibiotic residues in milk due to the use of rbST. In August 1993, Dr. Miller prepared an explanation of that analysis in order to make the difficult statistical concepts more comprehensible; her explanation was reviewed by Dr. Condon who agreed with its message. She gave copies of her document to the Acting Center Director, the head of the Office of New Animal Drug Evaluation (ONADE) and others. She stated that she did not know that her efforts would later be included in a package that went

²⁷ Monsanto and FDA/CVM officials met on July 12, 1993 to discuss the issue of post-approval monitoring.

ENCLOSURE

to brief Commissioner Kessler.

Finally, at a meeting that probably took place in mid-to-late August 1993, the Commissioner asked the Acting Center Director whom he would choose to take to a Congressional hearing to represent FDA's position, if the agency approved something. The Acting Center Director named Margaret Miller, at which point someone said that Dr. Miller had worked for Monsanto. This was the first time the Commissioner had heard of her prior Monsanto affiliation and he was reported to have been visibly surprised. He ordered an investigation into whether Dr. Miller had engaged in conduct creating a conflict of interest.

On November 4, 1993, FDA reported on its investigation. The agency concluded that although "Dr. Miller's participation in general bST matters does raise questions. . . she has not violated FDA's Standards of Conduct or the Office of Government Ethics Standards of Conduct."

Analysis of Dr. Miller's Activities after February 1993

The permanent regulatory prohibition on Dr. Miller's involvement with Monsanto's NADA ended when OGE's standards of conduct became effective on February 3, 1993. When the new rules became effective they replaced, by operation of law, most of FDA's ethical standards. The new regulations apply to an employee with a "covered relationship." By definition such a relationship with a former employer is limited to one year.²⁸ Since Dr. Miller had, by February, 1993, been at CVM for 3 years there was no continuing prohibition and no transgression of the standards.

At the same time it is true that both Commissioner Kessler and Dr. Miller expressed concern about her role in Posilac's approval. In that connection, we looked to see what role Dr. Miller had played in the agency's decision to approve the drug. We did not find any evidence that Dr. Miller participated in CVM's review of any of the NADA²⁹ or the Center's decision that the drug was approvable.

In early 1993, the FDA Commissioner reopened the issue of human food safety due to GAO concerns related to mastitis and antibiotic residue in

²⁸ 5 C.F.R. § 2635.502 (b)(1)(iv) (1994).

²⁹ Other than the concurrence she signed as previously discussed (see pages 10-11).

ENCLOSURE

milk. Senior CVM officials told us that they believed (1) these concerns were not warranted by the scientific evidence and (2) the drug to be approvable. As far as they were concerned the ultimate decision now rested with the Commissioner, although approval would officially take place at the Center. In order to explain to the Commissioner the issues involved in CVM's prior decision to approve Posilac -- which had been made without Dr. Miller's participation or influence -- senior CVM officials did enlist her expertise as described above.

Dr. Sechen

Dr. Sechen began her permanent employment at FDA in 1988 as an Animal Scientist. Before this, she had worked on several temporary assignments at the agency while she finished her graduate research at Cornell University. Her first temporary FDA appointment began in July 1986 and ended in November 1986, during which time she was on leave of absence from Cornell. Her duties included drug study reviews, and developing technical guidelines for rbST evaluation. Dr. Sechen's next two appointments were brief--3 days in January, 1987, and 20 days between August and November 1987. During these periods, Dr. Sechen updated FDA efficacy requirements for rbST, attended a workshop on rbST, and reviewed the efficacy data on rbST new animal drug applications.

Dr. Sechen's Ph.D. research consisted of three studies on metabolic changes in dairy cows caused by bST treatment, using compounds donated by Upjohn, American Cyanamid, and Monsanto. Two of the studies were performed prior to Dr. Sechen's first temporary assignment in July, 1986. A third study was conducted between March and August, 1987, using one of Monsanto's investigational rbST formulations.³⁰ The research was conducted pursuant to an agreement³¹ between Dr. Sechen's Cornell faculty adviser, Dr. Dale Bauman,³² and Monsanto.

³⁰ This was not the same formulation for which Monsanto sought approval, or that was eventually approved by FDA.

³¹ We examined the protocol submitted to Monsanto outlining the planned experiment and the terms of the agreement for Monsanto's donation.

³² Dr. Bauman did some consulting work for Monsanto. This work did not include preparation or review of any part of Monsanto's Posilac application. However, both Dr. Bauman and Monsanto officials confirmed that in his capacity as a consultant he

ENCLOSURE

According to Cornell University, Dr. Sechen was paid in the same manner as all other graduate students. Her stipend for approximately nine months of each year came from the state of New York. The remainder of the money came from unrestricted departmental funds in the Department of Animal Science.³³ Further, her advisor handled the contacts with Monsanto. Upon completion of the study, Dr. Sechen's advisor submitted the results and other data to Monsanto as required by FDA animal drug regulations.³⁴

When Dr. Sechen began working as a permanent FDA employee in February 1988, she became the primary reviewer for all rbST and other dairy production drug applications. In this capacity, Dr. Sechen assessed pivotal and non-pivotal study data³⁵ on drug effectiveness and animal safety, and coordinated reviews from other scientists in the areas of human health safety, environmental safety, and manufacturing chemistry. She also represented the Center for Veterinary Medicine at agency meetings and public forums, and provided a scientific basis for responding to congressional and consumer inquiries on rbST.

Between 1988 and 1990, Dr. Sechen was a primary author on 3 articles and co-author of 1 scientific article based on her graduate research on rbST which were published in peer-reviewed scientific journals between 1988 and 1990. In addition, for articles based on the study using Monsanto rbST, a memorandum from Dr. Sechen states that she and her faculty advisor submitted "the proposed publications to Monsanto about 30 days prior to submitting to a journal for their comments." In August 1992, Monsanto submitted these published articles to FDA as

provided the company with information on somatotropin that would have been useful to the prosecution of its drug application. In addition, according to Dr. Bauman, Monsanto agreed with Cornell to support several sometribove studies at the University. Dr. Bauman told us he was not compensated under these agreements. The results of these studies were published and Monsanto's support was mentioned. Some of these were submitted by Monsanto as pivotal studies in its NADA.

³³ According to Cornell University, unrestricted department funds are derived from farm income funds, foundation grants, alumni gifts, and friends of the department among other sources.

³⁴ 21 C.F.R. §511.1(b)(7)(iii) (1994).

³⁵ As was stated earlier, non-pivotal studies are reviewed for gross inconsistencies with pivotal data.

ENCLOSURE

non-pivotal data in support of the company's rbST application.

Analysis

Dr. Sechen never was a Monsanto employee. Her sole tie to the company prior to her permanent FDA employment was the use of an rbST compound in her graduate work. Dr. Sechen's advisor handled the substantive and administrative contacts with Monsanto. Thus, she would not have been covered by either FDA's permanent or one year ban, nor could she have had the covered relationship required by OGE's regulations. Therefore, we do not believe that she violated the conflict of interest rules.

In her official capacity as primary reviewer of sometribove, Dr. Sechen did evaluate two of her previously published articles. Her actions raise questions about the objectivity that she would be able to bring to her review of these articles. We note, however, that the articles did not evaluate the same drug formulation that was approved by the agency and they did not form part of a pivotal study and therefore were reviewed only for gross inconsistencies with the pivotal studies. These factors lead us to conclude that Dr. Sechen's review of her own articles had no effect on the drug's ultimate approval.

Mr. Taylor

Following his graduation from law school in 1976 and until May, 1980, Mr. Taylor was employed by the FDA's Office of Chief Counsel, where he was a legal advisor to the agency's Bureau of Medical Devices and Bureau of Foods, successively. From June, 1980, until the end of January, 1981, he was the Executive Assistant to the Commissioner, FDA. In February, 1981, he left FDA for the Atlanta-based law firm of King & Spalding. According to Mr. Taylor, he was hired by the firm as its first food and drug lawyer to handle the food law needs of a major client (The Coca Cola Company) and to develop a diversified food and drug practice. Mr. Taylor was a partner in the firm from July, 1984, until July, 1991, by which time he supervised a nine-lawyer food and drug group whose clients included Monsanto Agricultural Company. In July, 1991, Mr. Taylor left King & Spalding for the position of Deputy

ENCLOSURE

Commissioner for Policy at FDA.³⁶

With respect to his representation of Monsanto, Mr. Taylor told us that the company initially came to King & Spalding with a question about pesticide regulation and became a regular client thereafter. Although Mr. Taylor represented Monsanto on its plant biotechnology work, he said there was no issue involving labeling of specific products in connection with this work because a product was still years away. While with King & Spalding, he also prepared a memorandum for Monsanto as to whether it would be unconstitutional for various States to adopt different rules with respect to the use or labeling of rbST. He stated that he did not prosecute Monsanto's application for Posilac, which was handled by others in the firm.

New Animal Drug Application

Upon joining FDA in July, 1991, Mr. Taylor was counseled by the Health and Human Services Designated Agency Ethics Officer concerning potential conflicts of interest. On July 31, 1991, Mr. Taylor signed a memorandum in which he recused himself, for a period of one year, from participating in all particular matters--including "product approval applications"--in which listed former clients--including the Monsanto Company--were specific parties. These matters were to be referred either to the Associate Commissioner for Policy Coordination (William K. Hubbard) or to the Commissioner, FDA for action, without Mr. Taylor's participation.

Mr. Taylor told us that he advised Commissioner Kessler, Associate

³⁶ At the time he joined FDA, Mr. Taylor owned an investment partnership interest with certain attorneys at King & Spalding. The investment partnership's sole purpose was to hold stock of a corporate client (other than Monsanto) which the law firm had once received in payment for legal services. No other law firm assets had been added to the investment partnership. The question of conflict of interest arose because in a partnership, the financial interests of partners are imputed to other partners. Since Mr. Taylor's former law firm partners continued to represent industry regulated by FDA, he either had to sell his interest in the investment partnership or obtain a waiver. He was unable to sell his interest. Commissioner Kessler granted Mr. Taylor a waiver permitting him to hold the partnership interest because, (1) the interest represented a small portion of Mr. Taylor's net worth, (2) the viability of the investment partnership was not related to the success or failure of the law firm, and (3) the investment partnership was not engaged in activities that create inordinate loyalty to and financial dependence upon the other partners.

ENCLOSURE

Commissioner Hubbard, and others that he would not participate in discussions of Monsanto's application for Posilac because of his prior relationship with the firm. He said Monsanto's application may have been discussed at some of the daily morning meetings that Commissioner Kessler held, often by telephone, with his deputies. If the subject did come up, which he did not recall, Mr. Taylor said that he did not participate in the discussion.

Other FDA officials, including Commissioner Kessler, independently verified Mr. Taylor's lack of involvement in the approval of Monsanto's application for Posilac. Mr. Hubbard stated that he became involved in the rbST approval process because Mr. Taylor delegated the responsibility to him in order to avoid the appearance of a conflict of interest. Mr. Hubbard stated that Mr. Taylor made every effort not to get involved in rbST; for example, in staff meetings Mr. Taylor would ask the staff not to discuss rbST while he was there; and letters to Mr. Taylor which related to rbST were sent to Mr. Hubbard for action. More specifically, Mr. Hubbard also stated that Mr. Taylor was not involved in Monsanto's application for Posilac. Similarly, the Executive Assistant to the Commissioner stated that Mr. Taylor was not involved in the NADA process in any way. No one with whom we have spoken has had any knowledge of Mr. Taylor's involvement with, or even discussion about, Monsanto's application for Posilac.

Our review of the sometribove NADA file also shows no evidence of involvement by Mr. Taylor, either while he was with King & Spalding or at FDA. Absent some involvement in the FDA decision, there can be, by definition, no appearance of a loss of impartiality. Therefore, we conclude with respect to the NADA that Mr. Taylor's actions did not raise the appearance of a loss of impartiality.

INTERIM MILK LABELING GUIDANCE

Sometribove was approved on November 5, 1993 and on February 10, 1994, FDA published in the Federal Register, over Mr. Taylor's signature, guidance on the voluntary labeling of milk and milk products from cows that have not been treated with rbST.³⁷ We have reviewed the nature and extent of Mr. Taylor's involvement in the development of this

³⁷ "Interim Guidance on the Voluntary Labeling of Milk and Milk Products from Cows That Have Not Been Treated with Recombinant Bovine Somatotropin," 59 Fed. Reg. 6279 (1994).

ENCLOSURE

document to determine whether his activities may have created the appearance of a loss of impartiality.

The FDA Commissioner had long recognized that labeling would be a concern with rbST because it is produced using recombinant technology. According to FDA officials and documents, the Commissioner and Deputy Commissioner for Operations had questions regarding labeling at least as early as January 1993. At the time of sometribove's approval FDA announced that it had no basis on which to require labeling and that voluntary labeling would be permitted. Pressure from the states for further definition of what information could properly appear on a label increased until, following a meeting with Wisconsin's Secretary of Agriculture, Trade and Consumer Protection in December of 1993, FDA decided to begin drafting some form of guidance.

On February 10, 1994, FDA issued a guidance document stating that labeling a product as not having been produced from cows which had been treated with rbST was permissible, but warning that a "statement, which asserts that rbST has not been used in the production of the subject milk, has the potential to be misunderstood by consumers."

Guidance Chronology

The process for development of such types of guidance is informal and we have not been able to determine with precision when the decision was made to draft labeling guidance and who made that decision. From documents and our interviews with FDA officials, it appears that FDA's decision to begin drafting the guidance was driven by pressure from states to develop a nationwide policy. FDA officials traced this strong interest by the states in part to Commissioner Kessler's published remarks when sometribove was approved. At that time, the Commissioner stated that companies could voluntarily label milk products with respect to whether or not they were produced from cows treated with rbST as long as the labeling was not false or misleading.

Mr. Taylor attended a December 17, 1993 meeting where FDA officials discussed labeling in preparation for the Commissioner's meeting on the same topic with Wisconsin's Secretary of Agriculture, Trade and Consumer Protection on December 20, 1993. Sometime after this meeting, CFSAN employees began drafting milk labeling guidance in the

ENCLOSURE

form of a letter to the states.³⁸

Mr. Taylor met with CFSAN employees on January 6, 1994 to discuss the drafting process. The Center had outlined a general policy by this time. Center employees told us that it was their position that any labeling had to include sufficient context so that it would not be misleading.

Mr. Taylor met with CFSAN employees to go over the draft guidance on January 26, 1994. This meeting was intended to put the final touches on the guidance. The major point of concern to those present at the meeting was again how to place in the proper context a statement to the effect that milk had been produced without rbST. In essence, FDA officials felt that the bare statement "rbST free" would not only be false, but could lead people to believe that there was some compositional difference between milk produced with and without rbST. This would be misleading because CVM already had determined that the two products were essentially the same. On January 27, 1994, the policy was cleared by the Center and sent to FDA headquarters for final approval.

The decision to publish the guidance as a Federal Register notice was apparently made on February 2, 1994 after a meeting between the Commissioner, CFSAN officials and Michael Taylor. On February 4th, Mr. Taylor and other FDA officials took the draft interim guidance to the Office of Management and Budget and the Department of Agriculture to inform those agencies of FDA's plans. That weekend, the Commissioner called Michael Taylor to discuss the former's concerns about the need for additional discussion of context in the proposed guidance. The Commissioner's changes were made and became part of the final document.

Participants in the process characterized Michael Taylor's participation as ensuring that the process for making the decision operated smoothly. We were told by FDA officials that Mr. Taylor never sought to influence the thrust or content of the guidance. He was responsible for presenting FDA's proposed guidance to other parts of the government. Mr. Taylor told us that one reason for his involvement was the personal interest

³⁸ This assignment did not go to Office of Food Labeling, because its resources were concentrated on meeting the requirements of the Nutrition Labeling and Education Act of 1990; instead it was handled by the Office of Plant and Dairy Foods and Beverages, whose responsibility includes milk and milk products.

ENCLOSURE

that Commissioner Kessler took in the labeling issue.

Analysis

The OGE standards that took effect on February 3, 1993 are applicable to Mr. Taylor's involvement in development of the interim milk labeling guidance. As discussed above, these standards are directed at circumstances involving a covered relationship, which in this case would be Mr. Taylor's former representation of Monsanto. At the time the guidance was drafted, Mr. Taylor had been with the government for two and one-half years. Since, by definition, this type of covered relationship exists for only one year after a new employee enters government, Mr. Taylor was not covered by the appearance of loss of impartiality provisions.

Further, even if there had been a covered relationship between Mr. Taylor and Monsanto, Mr. Taylor's involvement did not present an appearance problem as that is defined under the OGE standards. The appearance standards apply to a "particular matter involving specific parties". A particular matter involving specific parties is defined under these circumstances as "judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, investigation, charge, accusation, arrest or other particular matter involving specific party or parties in which the United States is a party or has a direct and substantial interest."³⁹ This enumeration of matters generally involves instances of agency action involving a segregable transaction affecting the rights of a specific party or small group of people. This is different from a rulemaking or issuance of guidance which generally covers broad numbers of people in different transactional situations.

As described above, the voluntary milk labeling guidance is not a binding agency decision; rather it explains FDA policy and legal interpretations. In addition, the guidance -- prepared at the request of the states--covers milk labelers, who include food producers, farmers and stores. The guidance does not seem to be the type of agency action

³⁹ 5 C.F.R. § 2637.102(a)(7) (1994). See also, footnote 12 and surrounding text.

ENCLOSURE

that the impartiality standards cover.⁴⁰ Thus, we conclude that Mr. Taylor's involvement in the milk labeling guidance did not transgress the applicable ethics standards.⁴¹

⁴⁰ The HHS Designated Agency Ethics Official came to the same conclusion in his report to Commissioner Kessler on March 11, 1994. He wrote that the document was, "intended to explain FDA policy and legal interpretations governing a large and diverse group of affected food producers, farmers, and stores, as well as state regulatory authorities."

⁴¹ Mr. Taylor is a member of the Bar of the District of Columbia. His actions as an attorney are governed by the District of Columbia Rules of Professional Conduct. Because all attorneys owe a professional duty to their former clients we examined the applicable D.C. Rules of Professional Conduct. The first, Rule 1.9 (Conflict of Interest: Former Client), states:

"A lawyer who has formerly represented a client in a matter shall not thereafter represent another person in the same or a substantially related matter in which that person's interests are materially adverse to the interests of the former client unless the former client consents after consultation."

This rule on its face seems to require legal representation of both a prior and present client (See, *Derrickson v. Derrickson*, 541 A.2d 149 (D.C. 1988), in which the court held that Rule 1.9 was inapplicable because there was no prior attorney-client relationship.). While it is true that Mr. Taylor had represented Monsanto in private legal practice, as Deputy Commissioner for Policy at FDA, he was not acting as an attorney or as an employee of the HHS General Counsel's Office. HHS's "Statement of Organization, Functions and Delegations of Authority: Office of General Counsel, 51 Fed. Reg. 6319 (Feb. 21, 1986) states, "The General Counsel . . . [e]xercises general direction and supervision over all legal activities carried on by the Department."

Further, as we noted above (page 25) with respect to the milk labeling guidance Mr. Taylor did not in fact act as the agency's attorney. FDA's Office of Chief Counsel, which is part of HHS's Office of General Counsel, was responsible for the legal work done on the guidance. All participants in the milk labeling guidance process said that the interim guidelines were developed in cooperation between CFSAN and the Office of Chief Counsel. Mr. Taylor's role in the process was administrative. Therefore, we believe that Rule 1.9 is not applicable to this situation.

Assuming D.C. Rule 1.9 is inapplicable, D.C. Rule 1.6 (Confidentiality of Information) continues to apply to Mr. Taylor, as it does to all lawyers, after all representation has ended. See Rule 1.6(f). Rule 1.6(a) states:

"A lawyer shall not knowingly:

- 1) Reveal a confidence or secret of the lawyer's client;

ENCLOSURE

ARTICLE PUBLICATION

In the course of our review, we found that some of the articles published by Drs. Miller and Sechen related to scientific inquiries conducted on the effects of bovine somatotropin. Neither Dr. Miller nor Dr. Sechen received any compensation for the articles they published. Although HHS regulations then in effect⁴² encouraged employees to engage in outside writing,⁴³ the publication of these articles may have been contrary to FDA's requirements for prior approval of outside activities. As explained below, FDA publication requirements could easily have confused employees because of (1) CVM's own apparent lack of consistent policy on the matter and (2) differences between the regulatory requirements and FDA's public pronouncements. The purpose of the approval requirement is to avoid conflicts between government and outside work. Prior GAO and OGE opinions have cited outside activity reporting as a weakness in FDA's ethics programs, and our experience with CVM employees indicates that it continues to be a problem.

Publication Criteria

Prior to February 1993, HHS/FDA's writing regulations set forth standards relating to article publication and outside employment. The reach of these provisions depended upon the subject matter of the article and the employee's position at the agency. First, where the writing

-
- 2) Use a confidence or secret of the lawyer's client to the disadvantage of the client;
 - 3) Use a confidence or secret of the lawyer's client for the advantage of the lawyer or of a third person."

There was no indication in the record or in our discussions with FDA employees that Mr. Taylor had revealed or used any confidence of his former client Monsanto. Therefore, we do not believe that Mr. Taylor transgressed these rules.

⁴² The HHS writing regulations were replaced by OGE's standards in February 1993. HHS's reporting requirements for outside activities continue in effect until February 3, 1995. 59 Fed. Reg. 4779 (Feb. 2, 1994)

⁴³ 45 C.F.R. § 73.735-705(a) (1993) states in relevant part,

"Employees are encouraged to engage in outside writing and editing . . .

"

ENCLOSURE

activity was not related to the employee's official duties or other responsibilities and programs of the Federal government, then the only requirement was that employees either make no mention of their affiliation with FDA, or that the affiliation be used in such a way as to not suggest official endorsement of the work. Second, if the work was related to official duties or other government programs and responsibilities, then disclaimers were required.⁴⁴ Third, advance approval of the activity was required where the writing "pertains to subject matter directly related to an employee's official duties; (This includes editing for scientific or professional journals which is related to his or her official duties.)"⁴⁵

Although HHS/FDA's rules relating to writing have been superseded by OGE's standards, there is still a continuing requirement for employees to get approval for outside activities. Writing is included in both the HHS and OGE regulations under the regulatory sections on what constitutes an "outside activity."⁴⁶ HHS, in responding to a GAO report on outside activities, stated emphatically, "FDA requires approval for all outside activities."⁴⁷ This pronouncement is broader than the regulatory provisions which state that they apply only to "certain" outside activities.⁴⁸ If "all" activities are indeed covered, then CVM needs to so inform its employees.

In the course of our review, most employees we talked with did not

⁴⁴ 45 C.F.R. § 73.735-705(c) (1993).

⁴⁵ 45 C.F.R. §§ 73.735-705(d) (1993).

⁴⁶ 45 C.F.R. 73.705 Subpart G. (1993) and 5 C.F.R. 2635 Subpart H (1994).

⁴⁷ Employee Conduct Standards: Some Outside Activities Present Conflict-of-Interest Issues, GAO/GGD-92-34 (February 1992) at pg. 108. (emphasis in the original.) Similarly, a 1992 OGE report states that FDA requires prior approval for all outside activities.

⁴⁸ 45 C.F.R. § 73.735-708 (1993) reads as follows:

"(a) Scope. As specified in § 73.735-704 through 707, an employee is required to obtain advance administrative approval to engage in the following outside activities:

(1) Certain writing or editing activities"

ENCLOSURE

know when, if ever, they had to file an outside activity approval form for their writing activities. One employee was told to file a form only if the writing was for a for-profit journal. Two were unaware of any requirements. A third told us that if the work that was incorporated into an article had been done before the employee arrived at CVM and the employee only reviewed the article before publication, then there would not be a need to get prior outside approval for the activity. Confusion about outside activity reporting requirements is apparently a continuing problem at FDA. In 1988, OGE recommended that FDA provide guidance on approval of employees' outside professional and consulting services, public appearances, writing and editing. According to OGE, FDA approving officials did not understand the distinction between official duties and outside activities.⁴⁹

Articles Published by Drs. Miller and Sechen

We examined 11 articles, ten of which were published under FDA's old standards (See Appendix II for a complete list of the specific articles). These articles dealt with different aspects of bST and its effects. All were arguably related to the ongoing FDA review of Posilac. Only one of the articles was done pursuant to a valid outside activity request. Four of the articles carried no disclaimer, a statement that the article reflected the personal opinion of the writer and not that of the agency. In all cases, the publications listed the scientists' address as FDA.

Specifically, we looked at eight of the articles co-authored by Dr. Miller and published between August 1990 and November 1993. The publications dealt with somatotropin in cows and were not published under FDA's auspices. Dr. Miller developed all the information that was used in the articles before she left Monsanto.

Dr. Miller did not actually write the articles. She was listed as a co-author, as is the practice in scientific publishing, because the articles incorporated some of the work she had done while at Monsanto. The first listed, or primary author, is generally the person who did the actual writing. As a co-author, Dr. Miller usually received a copy of the article along with a copyright waiver form. The purpose of the waiver form was to obtain her statement that the information had not been published elsewhere as well as to receive any comments she might have on the

⁴⁹ See, Employee Conduct Standards, Some Outside Activities Present Conflict-of-Interest Issues, GAO/GGD-92-34 (February 1992) at pg. 78.

ENCLOSURE

article.

Dr. Miller told us that initially she did make comments on the articles, but stopped doing so when it became apparent to her that those comments were not being incorporated. Dr. Miller said that she understood that disclaimers had to be included in all articles that carried her address at FDA. We have verified with one primary author that this was Dr. Miller's practice. Nevertheless, one of the articles we examined did not contain a disclaimer.⁵⁰

We also examined three articles published by Dr. Sechen in 1989 and 1990. The articles were all based on Dr. Sechen's graduate work, dealt with somatotropin in cows and were not published under FDA's auspices. Dr. Sechen was the primary author on two of these publications. None of these articles were prepared pursuant to a request for outside activity and none contained a disclaimer. When asked, Dr. Sechen was unaware of any FDA requirements with respect to publishing, not an uncommon response at CVM.

While we did not find that the employees' lack of knowledge in this area had an effect on Monsanto's NADA, FDA should inform employees of their responsibilities to get approval of outside activities. It appears, based on the informal sample of CVM employees we interviewed, that FDA has not taken sufficient steps to solve the problems reported earlier by GAO and OGE. After reviewing a draft of this report, FDA informed us that it is taking steps to clarify its publishing requirements.

⁵⁰ According to Monsanto, the author of this article forgot to include the disclaimer.

ENCLOSURE

Appendix I

Our review included interviews with the following individuals:

Norris Alderson	Center for Veterinary Medicine (CVM)
Sheila Andrew	CVM
Alex Apostolou	No longer at CVM
Pat Arnall	Monsanto
Dale Bauman	Cornell University
Elizabeth Campbell	Center for Food Safety and Applied Nutrition (CFSAN)
Robert Cobb	Office of Government Ethics
Robert Condon	CVM
Catherine Copp	Department Health and Human Services (HHS)
Shellee Davis	CFSAN
Steven Denham	CVM
Philip Eppard	Monsanto
Suzanne Fitzpatrick	No longer at CVM
Lynn Friedlander	CVM
Robert Furrow	No longer at CVM
Susan Gilbert	District of Columbia Bar
Elizabeth Grove	CVM
Gerald Guest	No longer at CVM
Marina Hooten	HHS
William Hubbard	FDA
Roger Jones	CVM
David Kessler	FDA
Jack Kress	HHS
David Kowalczyk	Monsanto
John Kvenberg	CFSAN
Michael Landa	No longer at HHS
Robert Lake	CFSAN
Robert Livingston	CVM
Jerrold Mande	FDA
John Matheson	CVM
Margaret Miller	CVM
Cheryl Nimz	Journal of Dairy Science
Anita O' Connor	CVM
John O'Rangers	CVM
Janice Oliver	CFSAN
Mary Pendergast	FDA

ENCLOSURE

Terry Peters	CVM
Margaret Porter	HHS
Lucy Russell	No longer at HHS
F. Edward Scarborough	CFSAN
Suzanne Sechen	CVM
Fred Shank	CFSAN
J. Sedwick Sollers III	King & Spalding
David Steele	No longer at CVM
Jess Stribling	King & Spalding
Linda Suydam	FDA
Michael Taylor	No longer at FDA
Richard Teske	CVM
Rick Thomas	HHS
Sue Thorn	Journal of Endocrinology
Terry Troxell	CFSAN
John Vanderveen	CFSAN
Clydette Wantland	Journal of Dairy Science
Mitch Zeller	FDA

ENCLOSURE

Appendix II

List of articles published by Dr. Sechen and Dr. Miller that are discussed in this report.

Dr. Sechen:

Suzanne J. Sechen, Frank R. Dunshea, and Dale E. Bauman, *Somatotropin in lactating cows: effects on response to epinephrine and insulin*, 258 Am. J. of Physiology E582 (1990).

(Received 5/31/89. Accepted in final form 10/23/89. Published 4/90. Appears in NADA Vol 446, Tab 100).

W.S. Cohick, K. Plaut, S.J. Sechen, D.E. Bauman, *Temporal Pattern of Insulin-Like Growth Factor-I Response to Exogeneous Bovine Somatotropin in Lactating Cows*, 6(3) Domestic Animal Endocrinology 263 (1989).

(Received 1/3/89. Published 7/89). Appears in NADA Vol 446, Tab 102)

Suzanne J. Sechen, Dale E. Bauman, et al., *Effect of Somatotropin of Kinetics of Nonestrified Fatty Acid and Partition of Energy, Carbon and Nitrogen in Lactating Dairy Cows*, 72(1) J. of Dairy Science 59 (1989).

(Received 5/16/88. Accepted 8/23/88. Published 1/89)

There were no disclaimers in any of the articles published by Dr. Sechen, nor were we able to locate outside activity approval forms for any of these articles.

Dr. Miller:

P.J. Eppard, T.C. White, B.K. Birmingham, R. L.Hintz, L.A. Bente, D.C. Wood, W.J. Salsgiver, E. Rowold, M.A. Miller, et al., *Pharmacokinetic and Galactopoietic Response to Recombinant Variants of Bovine Growth Hormone*, 139 J. Endocrinology 441 (1993).

(Revised manuscript received 5/26/93. Published 12/93)

Mark A. McGuire, Dale E. Bauman, Margaret A. Miller, Gary Hartnell.

ENCLOSURE

Response of Somatomedins (IGF-I and IGF-II) in Lactating Cows to Variations in Dietary Energy and Protein and Treatment with Recombinant n-Methionyl Bovine Somatotropin, 122 J. Nutrition 128 (1992).

(Received 4/19/91. Accepted 7/2/91. Published 1/92)

F.A. Adriaens, M.A. Miller, et al., *Long-Term Effects of Somatotropin in Lactating Cows During a Fourth Consecutive Lactation of Treatment: Insulin and Somatotropin Responses to Glucose Infusion*, 75(2) J. of Dairy Science 472 (1992).

(Received 12/12/90. Accepted 9/23/91. Published 2/92.)

W.J. Cole, P.J. Eppard, B.G. Boysen, K.S. Madsen, R.H. Sorbet, M.A. Miller, et al., *Response of Dairy Cows to High Doses of a Sustained-Release Bovine Somatotropin Administered During Two Lactations. 2. Health Reproduction*, 75(1) J. of Dairy Science 111 (1992).

(Received 11/15/90. Accepted 8/29/91. Published 1/92.)

P.J. Eppard, G.J. Rogan, B.G. Boysen, M.A. Miller, et al., *Effect of High Doses of a Sustained-Release Bovine Somatotropin on Antibody Formation in Dairy Cows*, 75(11) J. of Dairy Science 2959 (1992).

(Received 1/29/92. Accepted 6/2/92. Published 11/92.)

John L. Vicini, Frances C. Buonomo, Jeffrey J. Veenhuizen, Margaret A. Miller, et al., *Nutrient Balance and Stage of Lactation Affect Responses of Insulin, Insulin-Like Growth Factors I and II, and Insulin-Like Growth Factor-Binding Protein 2 to Somatotropin Administration in Dairy Cows*, 121 J. Nutrition 1656 (1991).

(Received 12/7/90. Accepted 4/1/91. Published 10/91.)

Robert J. Collier, M.A. Miller, et al., *Factors Affecting Insulin-Like Growth Factor-I Concentration in Bovine Milk*, 74(9) J. of Dairy Science 2905 (1991).

(Received 8/9/90. Accepted 3/26/91. Published 9/91.) There was no disclaimer for this article.

ENCLOSURE

J.L. Vicini, S. Hudson, M.A. Miller, et al., *Effect of Acute Challenge with an Extreme Dose of Somatotropin in a Prolonged-Release Formulation on Milk Production and Health of Dairy Cattle*, 73(8) J. of Dairy Science 2093 (1990).

(Received 10/16/89. Accepted 3/7/90. Published 8/90.) At the time this article was accepted for publication, Dr. Miller had a valid outside activity approval form.