



SEP 29 1994

Memorandum

Date

From

June G Brown
June Gibbs Brown
Inspector General

Subject

Follow-up Review of Possible Improper Pre-Approval Promotion Activities (A-15-93-00018)

To

Philip R. Lee, M.D.
Assistant Secretary for Health

The attached final report provides you with the results of our follow-up review of our May 1991 report entitled, "Need for the Food and Drug Administration to Review Possible Improper Pre-Approval Promotional Activities" (A-15-91-00007). The objective of our May 1991 review was to look at possible pre-approval promotion of bovine somatotropin (bST), a new animal drug developed to increase milk production in cows, which was still under review by the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM). Congressman Bernard Sanders requested that we conduct this follow-up because of his concerns about CVM's response to Monsanto Agricultural Company's (Monsanto) sponsorship of possible pre-approval promotion activity occurring since our May 1991 report was issued. Monsanto's bST product was approved by FDA in November 1993.

We specifically examined: (1) corrective action taken in response to recommendations contained in our May 1991 report; (2) action taken for possible pre-approval promotion occurring during recent Monsanto-sponsored activities; (3) criteria available for reviewing potential cases of pre-approval; and (4) the range of regulatory actions that can be taken if such promotion occurs.

Our analysis showed that CVM took appropriate corrective action in anticipation of recommendations made in our May 1991 report. In addition, CVM appropriately concluded that, overall, Monsanto-sponsored focus groups and a video produced beginning in December 1992 did not violate the intent of the Federal regulation found at 21 Code of Federal Regulations 511.1(b)(8)(iv). However, we also found that CVM should have, and did not, issue a warning letter stating that regulatory action would be taken should violative activities occurring at a January 1993 university seminar continue. We also found--and CVM itself acknowledges--that the Federal regulation should be revised to directly describe what constitutes allowable promotional activities. Should a drug company

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undertake improper promotional activities, CVM may take certain regulatory actions under the Federal statute.

This report contains recommendations to ensure that the Federal regulation governing pre-approval promotion is revised, in part, to address activities that sponsors can undertake while still being in compliance with this regulation.

The Public Health Service generally agreed with the report's contents and recommendations. It indicated that CVM is currently revising the regulation and developing internal guidelines on promotion and advertising.

We would appreciate being advised of any further action taken or contemplated on our recommendations within the next 60 days. If you have any questions, please call me or have your staff contact Michael R. Hill, Assistant Inspector General for Public Health Service Audits, at (301)443-3582.

Attachment

cc:
David A. Kessler, M.D.
Commissioner of Food and Drugs

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**FOLLOW-UP REVIEW OF POSSIBLE
IMPROPER PRE-APPROVAL PROMOTION
ACTIVITIES**



JUNE GIBBS BROWN
Inspector General

SEPTEMBER 1994
A-15-93-00018

EXECUTIVE SUMMARY

Congressman Bernard Sanders requested that the Office of Inspector General (OIG) conduct a follow-up to our May 1991 report entitled, "Need for the Food and Drug Administration to Review Possible Improper Pre-Approval Promotional Activities" (A-15-91-00007). The objective of our May 1991 review was to look at possible pre-approval promotion of bovine somatotropin (bST), a new animal drug developed to increase milk production in cows, which was still under review by the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM). Congressman Sanders requested that we conduct this follow-up because of his concerns about CVM's response to Monsanto Agricultural Company's (Monsanto) sponsorship of possible pre-approval promotion activity occurring since our May 1991 report was issued. Monsanto's bST product was approved by FDA in November 1993.

Our overall objective was to conduct a follow-up review of CVM's oversight of possible pre-approval promotion of unapproved new animal drugs. Based on Congressman Sanders' specific concerns, our subobjectives were to answer the following questions:

- Did CVM take appropriate corrective action in response to recommendations contained in our May 1991 report?
- Did CVM take appropriate action for possible pre-approval promotion during three separate activities Monsanto sponsored since our May 1991 report?
- Does CVM have adequate criteria for reviewing potential cases of pre-approval promotion?
- What are the actions CVM can take if it determines that pre-approval activities have occurred?

In general, we found that CVM made appropriate conclusions when reviewing possible pre-approval promotion activities occurring since May 1991. However, we believe--and FDA agrees--that revising the Federal regulation would strengthen the agency's oversight of pre-approval promotion activities.

With respect to our specific subobjectives, we found that:

- the CVM took appropriate corrective action, as recommended in our May 1991 report, in the form of regulatory letters¹ and correspondence² to bST sponsors and the Animal Health Institute (AHI) requesting conformance to Federal regulation 21 Code of Federal Regulations (C.F.R.) 511.1(b)(8)(iv).
- the CVM appropriately determined that regulatory action was not warranted because, overall, Monsanto-sponsored focus groups and a video produced beginning in December 1992 did not violate the intent of the Federal regulation. However, CVM should have issued a warning letter³ for violative activities taking place at a 1993 seminar at Louisiana State University Agricultural Center (LSU).
- Federal regulation 21 C.F.R. 511.1(b)(8)(iv) does not contain wording that enables CVM to provide regulatory criteria directly defining pre-approval promotion and allowable activities.
- should a drug company undertake pre-approval promotion activities, the Federal statute provides CVM with a range of regulatory actions that can be taken.

We recommend that you direct the Commissioner of the FDA to:

- ensure that revisions are made to 21 C.F.R. 511.1(b)(8)(iv), in part, to address various pre-approval promotion activities sponsors can conduct while being in compliance with this Federal regulation and to increase the prominence of the regulation; and
- develop criteria, formal staff guidelines, and policies, based on revisions to the Federal regulation, to be used for CVM review of potential pre-approval promotion activities.

¹In accordance with FDA terminology, we use the term "regulatory letters" to refer to letters written before May 1991 identifying specific violations of statutes or regulations for which sanctions may be taken.

²We use the term "correspondence" to refer to CVM's letters issued in response to Monsanto and other drug companies' concerns about violative activities described in CVM's 1991 regulatory letters.

³After May 1991, FDA changed the term "regulatory letter" to "warning letter."

The Public Health Service (PHS), in its July 25, 1994 comments (see Appendix) on our draft report, generally agreed with the report's contents and recommendations. In concurring with both recommendations, PHS stated that CVM is currently revising the regulation and developing internal guidelines on promotion and advertising.

The PHS disagreed with our conclusion that CVM should have issued a warning letter for a Monsanto representative's presentations at a LSU seminar, and brought to our attention FDA's draft policy statement on industry-supported scientific and educational activities and a related lawsuit. After reviewing these documents, we determined that they do not alter our conclusion regarding the need for a warning letter to be issued to Monsanto for its LSU presentations.

OTHER AUDIT REPORTS

Need for the Food and Drug Administration to Review Possible Improper Pre-Approval Promotional Activities, May 1991 (A-15-91-00007)

Audit of Issues Related to the Food and Drug Administration Review of Bovine Somatotropin, February 1992 (A-15-90-00046)

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INTRODUCTION

Congressman Sanders requested that OIG conduct a follow-up to our May 1991 report on possible pre-approval promotion of bST, a new animal drug developed to increase milk production in cows, which was still under review by FDA's CVM. In our May 1991 report entitled, "Need for the Food and Drug Administration to Review Possible Improper Pre-Approval Promotional Activities" (A-15-91-00007), we recommended that CVM take corrective actions related to drug sponsors' activities which appeared to violate the Federal regulation governing pre-approval promotion of new animal drugs. This follow-up was requested because of Congressman Sanders' concerns about CVM's response to Monsanto's sponsorship of possible pre-approval promotion activity occurring since our May 1991 report was issued.

BACKGROUND

On November 5, 1993, FDA approved the use of Monsanto's bST product as safe and effective for increasing the production of milk in dairy cows. Natural bST is a hormone produced by the pituitary gland of cows and helps to control milk production. Using recombinant deoxyribonucleic acid (DNA) technology,⁴ bST has been artificially produced for injection into dairy cows to increase their milk production.

In the early 1980's, FDA's CVM, Division of Biometrics and Production Drugs, began reviewing the safety and effectiveness of bST, also referred to as bovine growth hormone. Four drug sponsors originally filed applications with CVM to obtain approval to commercially market their formulations of bST.

The Federal regulation found at 21 C.F.R. 511.1(b)(8)(iv) specifically prohibits a drug sponsor, or any other person acting for the sponsor, from representing the drug as safe and effective for the purposes for which it is under investigation. The regulation further provides that this prohibition "...is not intended to restrict the full exchange of scientific information." During the application process, FDA provides drug sponsors with an investigational exemption so that an unapproved drug can be shipped to sites for conducting scientific studies necessary for approval. The CVM's Division of Surveillance is responsible for reviewing possible pre-approval promotion activities.

During its review of Monsanto-sponsored pre-approval promotion activities, CVM examined market research guidelines developed by FDA's Center for Drug Evaluation and Research's (CDER) Division

⁴A technology using bacteria to synthesize substances usually produced by mammals.

of Drug Marketing, Advertising, and Communications (Division). This Division is responsible for reviewing possible pre-approval promotion of human drugs. Officials from this Division have been involved in developing guidelines to distinguish reasonable market research activities from promotion activities that are in violation of the Federal regulation of pre-approval promotion of human drugs. The CVM discussed these market research guidelines with CDER officials to determine whether such criteria could be applied to CVM pre-approval promotion situations.

In May 1991, as part of our work on a request from Congressman John D. Conyers, Jr., Chairman, House Committee on Government Operations, OIG issued a report entitled, "Need for the Food and Drug Administration to Review Possible Pre-approval Promotional Activities" (A-15-91-00007), alerting CVM to a possible violation of the Federal regulation pertaining to the pre-approval promotion of bST. In responding to our December 1990 draft report, CVM agreed that certain material disseminated by Monsanto, the other bST sponsors, and AHI, a trade group representing veterinary drug firms, required corrective action. In its response, CVM stated that a pre-approval promotion review was already underway and corrective action would be taken.

OBJECTIVES, SCOPE, AND METHODOLOGY

Objectives

Our overall objective was to conduct a follow-up review of CVM's oversight of possible pre-approval promotion of unapproved new animal drugs. Based on Congressman Sanders' specific concerns, our subobjectives were to answer the following questions:

- Did CVM take appropriate corrective action in response to recommendations contained in our May 1991 report?
- Did CVM take appropriate action for possible pre-approval promotion during three separate activities Monsanto sponsored since our May 1991 report?
- Does CVM have adequate criteria for reviewing potential cases of pre-approval promotion?
- What are the actions CVM can take if it determines that pre-approval activities have occurred?

Scope

Our review was conducted at CVM offices in Rockville, Maryland, during the period from March to October 1993, in accordance with generally accepted government auditing standards.

During our review, we identified and analyzed three separate cases of possible pre-approval promotion reviewed by CVM. These three Monsanto-sponsored activities occurred during the time period between May 1991 through October 1993. The CVM did not find evidence of any other possible pre-approval promotion activities occurring since our May 1991 report was issued.

The three cases of possible pre-approval promotion on the part of Monsanto are:

--Focus Groups:

December 1992 focus groups were conducted in Riverside, California; Bellingham, Washington; and Tampa, Florida; and were also planned for additional locations. These group interviews, conducted by a market research consultant under contract to Monsanto, each consisted of 10 to 12 dairy farmers who were paid approximately \$100 for participating in a discussion about a proposed bST product.

--Videotape:

"bST and Milk-Issues and Answers," a video produced beginning in December 1992, by Image Base in cooperation with the American Medical Association. The videotape showed researchers and experts, including officials from the American Medical Association, American Society of Pediatrics, National Institutes of Health, and a former Director of FDA's Center for Food Safety and Applied Nutrition, discussing bST's safety and effectiveness. The video was scheduled to be shown on cable television after bST approval. However, one copy of the video was released, without authorization, prior to bST approval.

--University Seminar:

January 1993 LSU seminar presentations by a Monsanto representative. Slides were shown and an article about bST was handed out during the seminar. Participants included persons involved in the dairy industry.

Methodology

To conduct our follow-up review, we examined corrective action taken in response to our May 1991 report. We also reviewed CVM's actions in response to possible pre-approval promotion activities occurring since our May 1991 report. In addition, we examined CVM's criteria for reviewing such activities, as well as regulatory responses that can be taken if pre-approval promotion occurs.

To examine corrective action CVM took in response to recommendations contained in our May 1991 report, we reviewed regulatory letters and correspondence with drug sponsors. In anticipation of our final May 1991 report, CVM issued its first regulatory letter stating that drug sponsors must conform to Federal regulation 21 C.F.R. 511.1(b)(8)(iv). Its most recent correspondence regarding activities allowed under this regulation was issued in May 1993.

To examine CVM's conclusions about possible pre-approval promotion activities sponsored by Monsanto, we reviewed video and audiotapes of the December 1992 focus groups as well as materials handed out to the participants. We also viewed a copy of the videotape, "bST and Milk-Issues and Answers," and examined materials handed out at the January 1993 LSU seminar. In addition, we interviewed CVM officials responsible for carrying out reviews of these activities. When reviewing CVM's conclusions regarding action warranted for the December 1992 focus groups, we discussed market research criteria pertaining to human drugs with officials from FDA's CDER.

To conduct our analysis of criteria for reviewing potential pre-approval promotion activities, we examined the Federal regulation governing such activities. We also interviewed FDA regulatory officials to gain their perspectives on the need for revisions and strengthening of this regulation. In addition, we examined FDA's proposed revisions for this regulation.

To determine the range of appropriate regulatory responses CVM can take if pre-approval promotion occurs, we discussed possible regulatory actions with officials responsible for reviewing such activities. We also discussed the range of penalties and sanctions that may be taken.

To gain industry's perspective, we met with Monsanto representatives to discuss their views regarding CVM's conclusions about possible pre-approval promotion activities. We also discussed with them the need for revisions to the Federal regulation governing such activities.

FINDINGS

Our follow-up review, conducted in response to Congressman Sanders' concerns about CVM's oversight of possible pre-approval promotion activities by bST sponsors, found that:

- the CVM took appropriate corrective action in anticipation of OIG's May 1991 report, by issuing regulatory letters and correspondence stating that bST drug sponsors and AHI must comply with the Federal regulation governing pre-approval promotion activities.
- the CVM appropriately determined that regulatory action was not warranted because, overall, Monsanto-sponsored focus groups and a video produced beginning in December 1992, did not violate the intent of the Federal regulation. However, CVM should have issued a warning letter for violative activities taking place at a 1993 LSU seminar.
- Federal regulation 21 C.F.R. 511.1(b)(8)(iv) does not provide criteria directly defining pre-approval promotion and allowable activities.
- should a drug company undertake pre-approval promotion activities, the Federal statute provides CVM with a range of regulatory actions that can be taken.

The CVM took appropriate corrective action in anticipation of OIG's May 1991 report

The CVM took appropriate corrective action in anticipation of our May 1991 report by issuing regulatory letters to Monsanto, other sponsors, and AHI stating that they must comply with the Federal regulation concerning pre-approval promotion activities. Beginning in January 1991, CVM issued regulatory letters providing samples of objectionable materials previously disseminated by bST sponsors. It also replied to sponsors' concerns about violative activities described in these initial letters through additional correspondence to these drug companies and AHI.

The first step in taking corrective action for possible pre-approval promotion activities is to notify the sponsor so that the situation can be corrected immediately. The CVM began this corrective action by issuing a regulatory letter to Monsanto in January 1991. In this and similar letters to other bST sponsors and AHI, CVM requested that Monsanto conform to the Federal regulation governing pre-approval promotion activities by:

"...immediately stopping the use of all materials that may lead persons to believe that bST is safe and effective for purposes which are still under investigation."

These regulatory letters contained samples of objectionable materials previously disseminated by sponsors. These materials included the following statements:

"...bST allows dairymen to produce more milk from existing herds or maintain the same production levels from smaller herds.

"...bST should help farmers lower their production costs.

"...a variety of academic and industrial research involving hundreds of cows had disclosed no observed differences in body weight, physical condition, susceptibility to disease or overall health of the cows as a result of bST use...."

In response to these regulatory letters, bST sponsors and AHI expressed concern that CVM's description of violative activities infringed on their ability to engage in allowable exchanges of scientific information. The CVM replied through a series of meetings and additional correspondence, the latest of which was issued in May 1993. In its correspondence, CVM stated that, while drug sponsors could participate in scientific exchanges of information, they must clearly articulate that there are areas for which bST is still under investigation to determine its safe and effective use in animals. The CVM's correspondence also warned that regulatory action would be taken if drug sponsors did not comply with the Federal regulation concerning pre-approval promotion.

The CVM appropriately concluded that two Monsanto-sponsored activities, overall, did not violate the intent of the Federal regulation; a warning letter should have been issued for presentations given by a Monsanto representative

The CVM appropriately concluded that Monsanto-sponsored focus groups and a video produced beginning in December 1992, did not violate the intent of Federal regulation 21 C.F.R. 511.1(b)(8)(iv). However, we believe that CVM should have issued a warning letter regarding improper promotional information provided by a Monsanto representative during presentations at an LSU seminar.

Regulatory action not warranted
for December 1992 Focus Groups

We found that CVM appropriately determined that Monsanto-sponsored focus groups conducted in December 1992, while containing some elements of promotion, were essentially held for market research purposes. Although regulatory action was thus not warranted in this case, we believe that CVM was prudent in endorsing Monsanto's decision to cease its pre-approval market research. Monsanto voluntarily discontinued its focus group meetings after the December 1992 sessions. However, we believe that CVM should have notified Monsanto that handouts used during these focus groups violated the Federal regulation governing pre-approval promotion.

The CVM concluded that regulatory action was not warranted because these focus groups were legitimate market research activities and not intended, overall, for promotional purposes. In a January 1993 letter to Monsanto, CVM found that "...termination was not legally required," although the company's discontinuation of the sessions was "prudent." In applying criteria CDER used to review compliance with a similar regulation governing pre-approval promotion of drugs for human use, CVM found:

- the preponderance of information flow was from the participants to the facilitator and the sponsor;
- the activity was conducted by a professional focus group facilitator, and participants were paid a substantial fee; and
- the activity involved a limited number of participants and sessions.

While we do not question this overall conclusion, we believe that CVM should have, but did not, clearly notify the company that use of certain printed handouts as part of the focus groups violated Federal regulation 21 C.F.R. 511.1(b)(8)(iv). The CVM acknowledged, in a January 1993 letter to Congressman Sanders, that "...a promotional type print visual aid (showing the proposed tradename and the sponsor's name) was presented." However, in its January 1993 letter to Monsanto, CVM did not identify the visual aid, which we determined was a handout provided to focus group participants, citing the advantages of bST.

We found that the handout referred to above, and at least one other handout provided to the focus group participants, represented bST as safe and effective for areas still under investigation. For example, the handout referred to above contained statements and data showing that bST use does not affect the incidence of mastitis (udder infection) or pregnancy rates in treated cows. This handout also showed increased milk

production resulting from bST use. According to CVM's January 1991 regulatory letter and subsequent correspondence to Monsanto, the dissemination of materials containing such statements clearly violated Federal regulation 21 C.F.R. 511.1(b)(8)(iv). The fact that the handouts were returned to the focus group leader before the end of the sessions does not appear to mitigate the promotional nature of the handouts.

We believe that in order to deter future violations by the industry, CVM should have notified Monsanto that the use of such handouts constituted a violation of the Federal regulation governing pre-approval promotion. However, since Monsanto volunteered to discontinue the focus groups, we do not believe that CVM should impose regulatory sanctions upon the company.

Appropriate action taken for videotape produced beginning in December 1992

In the second case of possible pre-approval promotion, involving a Monsanto-sponsored videotape on bST, we found that CVM appropriately determined that the firm did not intend to promote bST through the unintentional release of a video in which the drug was portrayed as safe and effective. Although regulatory action was not indicated in this case, CVM recommended action to better safeguard the video's dissemination before product approval.

We noted--and CVM acknowledged--that the video contained representations of bST as safe and effective for areas still under review. We agree with CVM's decision not to take regulatory action, however, because it appears that Monsanto did not intend to release the video before the product was approved. We agree with CVM that there was no evidence to suggest that Monsanto condoned the unauthorized release of one of the videos. The fact that the video was not distributed in a promotional context to potential customers is a further indication that Monsanto did not intend to violate the Federal regulation.

We believe that CVM recommended appropriate action for deterring future unauthorized release of marketing materials before approval. For example, CVM cautioned Monsanto against sharing videotapes with organizations not involved in the video production. In addition, CVM advised that formal, written requests of confidentiality be given to all organizations receiving preview copies of videotapes, not just some of them.

Warning letter should have been issued for LSU seminar presentations

Regarding the third case of possible pre-approval promotion that came to CVM's attention since our report was issued in May 1991--presentations by a Monsanto representative at a LSU seminar--we

determined that CVM had a legitimate basis for sanctioning Monsanto and that CVM should have communicated this in a warning letter. Instead, we believe that CVM's correspondence with the company could have been interpreted as excusing the conduct.

Based on its review of the LSU seminar materials, CVM concluded that Monsanto represented bST in a promotional manner by implying that the drug had been proven safe and effective for increasing milk production in cows. In its October 1993 letter to Monsanto, CVM specifically stated that: (1) several of the slides used in the seminar referred to increased milk production as a result of bST use; and (2) the leader of the seminar disseminated, apparently without being requested, an article representing bST as safe and effective. Based on this analysis, CVM advised the firm to:

- examine its March 1992 and May 1993 letters containing guidance on the types of information dissemination activities that were and were not permissible for unapproved new animal drugs; and
- take steps to preclude further objectionable activity.

Our analysis of the guidelines provided in the two letters recommended for Monsanto's review shows that they are consistent with CVM's previous letters describing permissible and not permissible information dissemination activities. The March 1992 CVM letter pre-dated the LSU seminar, and, therefore, should have been adequate forewarning to Monsanto about the range of permissible activities. We therefore dispute CVM's apparent view that Monsanto's activity was in some way excused because of a lack of adequate guidance.

Our review of Monsanto's focus groups and a videotape produced beginning in December 1992 showed that Monsanto did not intend to violate the Federal regulation of pre-approval promotion, and overall, its activities appeared to be in compliance with this regulation. However, with respect to Monsanto's activity at LSU, our review of the handout provided to participants and a description of the slides used showed that improper promotion activities took place at this seminar. In our view, these materials were clearly not necessary for the "...full exchange of scientific information."

In sum, we believe that CVM's October 1993 letter to Monsanto inappropriately excused violative activities which took place at the LSU seminar. Therefore, we believe that CVM should have taken stronger action by issuing a warning letter stating that specific regulatory action would be taken should such violative activity continue.

Federal regulation of pre-approval promotion
should be revised and strengthened

The Federal regulation governing pre-approval promotion does not contain wording to directly define pre-approval promotion and allowable activities. We believe--and CVM itself acknowledges--that the Federal regulation pertaining to pre-approval promotion, 21 C.F.R. 511.1(b)(8)(iv), should be revised to directly address the variety of activities that may involve pre-approval promotion. Our discussion with Monsanto representatives revealed that they also believe that this Federal regulation should be revised.

Federal regulation 21 C.F.R. 511.1(b)(8)(iv) states that a new animal drug cannot be represented as being safe and effective for purposes for which it is under investigation, but it does not contain the words "pre-approval promotion," nor does it give information on acceptable activities that can be undertaken by animal drug sponsors. The regulation states that it is not intended to restrict scientific information, but does not explain what activities can be used for this exchange of information.

We believe--and CVM agrees--that regulatory change is needed. In fact, CVM's Division of Compliance, Petition and Regulations Branch is currently drafting revisions to the pre-approval promotion regulation, as part of the revision to the body of regulations contained in 21 C.F.R. 511.1, New Animal Drugs for Investigational Use. Although these revisions are in a preliminary stage and are not ready for publication, officials told us that possible revisions include adding the wording "promotion" and "market research." In addition, this section may be made more prominent through the use of a subtitle.

Monsanto representatives told us that Federal regulation 21 C.F.R. 511.1(b)(8)(iv) should be revised because it does not provide sufficient clarification or guidance regarding allowable activities. These representatives suggested that the wording used in this regulation should be similar to the more direct wording used in the Federal regulation governing human drug pre-approval promotion.

Range of appropriate regulatory
actions for pre-approval promotion

In response to Congressman Sanders' question about actions FDA can take if a drug sponsor is found to have conducted improper pre-approval promotion activities, we found that the agency, under statute, has several regulatory options. These options include: (1) notifying the drug sponsor and requesting immediate correction; (2) terminating the investigational exemption granted by FDA which allows the shipment of unapproved drugs to sites for conducting scientific studies necessary for approval; (3) seizing

shipments of the investigational drug; (4) filing an injunction to stop promotion activities; and/or (5) initiating criminal proceedings. According to FDA, however, termination of the investigational exemption for drugs such as bST would have little impact since the results of studies already conducted during the application process would still be valid.

CONCLUSIONS

Our follow-up review of possible pre-approval promotion of bST shows that FDA's CVM generally took appropriate action in response to possible pre-approval activities by bST sponsors. However, we believe--and FDA agrees--that revising the Federal regulation governing such activities would allow the agency to apply more specific criteria for reviewing compliance with this regulation. As the three cases of possible pre-approval promotion discussed in this report show, CVM has been called upon to review a variety of potential promotion activities. Had there been more specific regulatory criteria, such cases of potential pre-approval promotion, and the need for CVM to review them, might then have been avoided.

Pre-approval promotion may lead to public misperceptions about a drug's safety and effectiveness, and could help a sponsor gain a competitive marketing advantage upon FDA's approval of the drug. Therefore, regulatory action should be taken if warranted. We believe that revising the Federal regulation is the best way to apprise the animal drug industry as to the applicable criteria on allowable pre-approval promotion activities.

RECOMMENDATIONS

We recommend that you direct the Commissioner of FDA to:

- ensure that revisions are made to 21 C.F.R. 511.1(b)(8)(iv), in part, to address various pre-approval promotion activities sponsors can conduct while being in compliance with this Federal regulation and to increase the prominence of the regulation; and
- develop criteria, formal staff guidelines, and policies, based on revisions to the Federal regulation, to be used for CVM review of potential pre-approval promotion activities.

PHS COMMENTS AND OIG RESPONSE

In its July 25, 1994 comments, PHS generally agreed with the draft report's contents and recommendations. In concurring with both recommendations, PHS stated that CVM is currently revising the regulation and developing internal guidelines on promotion and advertising.

The PHS disagreed, however, with our conclusion that CVM should have issued a warning letter to Monsanto for the LSU seminar. It stated that the LSU issue was "...sufficiently unclear and that a warning letter would not be supported." Based on our understanding of the LSU situation and previously issued letters to Monsanto regarding pre-approval promotion, we continue to believe that a warning letter would have been appropriate and supportable in this case. The OIG, however, is not suggesting that FDA take the action at this time.

In its general comments, PHS also pointed out that the draft report did not consider a Federal Register notice, dated November 27, 1992, containing FDA's draft policy statement on industry-supported scientific and educational activities. The draft policy statement delineates categories of educational activities that may continue to be funded by industry and yet avoid regulation as advertising or promotional labeling. The PHS states in its general comments that FDA is being sued over the issue of industry-sponsored continuing medical education, and that in light of such litigation, "...CVM was correct in its assessment."

The FDA did not inform OIG of the draft policy statement or lawsuit during our review. However, after recently reviewing the draft policy statement, we do not believe that it alters our conclusion that CVM should have issued a warning letter to Monsanto. Assuming that the policy statement is intended to govern the pre-approval promotion of a product, the statement distinguishes between scientific and educational activities "...performed by or on behalf of the company..." that markets the product, which would be subject to regulation, and those activities which are "...independent of the substantive influence of a company..." which should not be regulated.

In the LSU situation, where we found that CVM should have issued a warning letter, the presentations in question were conducted by a representative of Monsanto, which produced the drug in question. Thus, there would be no issue of whether the presentations were "influenced" by the company. The draft policy statement does not diminish FDA's responsibility to regulate the pre-approval promotion of investigational drugs when such promotion is conducted by the drug company itself.

We would appreciate being advised within 60 days of the status of corrective actions taken or planned on each recommendation. Should you wish to discuss the issues or recommendations contained in this report, please call me or have your staff contact Michael R. Hill, Assistant Inspector General for Public Health Service Audits, at (301)443-3582.

APPENDIX



MEMORANDUM

Rockville MD 20857

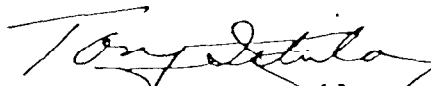
Date: JUL 25 1994

Subject: Deputy Assistant Secretary for Health Management
Operations

Subject: PHS Comments on Office of Inspector General (OIG)
Draft Report "Follow-Up Review of Possible Improper
Pre-Approval Promotion Activities," A-15-93-00018

To: Inspector General, OS

Attached are the PHS comments on the subject draft report. We are in general agreement with the report's contents and recommendations. Our comments describe our concerns regarding some of the auditors' conclusions and the actions the Food and Drug Administration is taking to implement the recommendations.


Anthony L. Itteilag

Attachment

COMMENTS OF THE PUBLIC HEALTH SERVICE ON THE OFFICE OF
INSPECTOR GENERAL (OIG) DRAFT REPORT "FOLLOW-UP REVIEW OF
POSSIBLE IMPROPER PRE-APPROVAL PROMOTION ACTIVITIES,"
A-15-93-00018, JUNE 1994

General Comments

We are in general agreement with the OIG draft report's contents and recommendations. However, we disagree with some of the details contained in the body of the report. We disagree with the OIG suggestion that the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) should have issued a Warning Letter to Monsanto Agricultural Company (Monsanto) in response to its activity at the Louisiana State University seminar. The CVM assessment of the situation was quite different than that portrayed in the OIG draft report. The CVM concluded that this issue was sufficiently unclear and that a Warning Letter would not be supported.

Furthermore, the OIG draft report does not mention that FDA had published in the November 27, 1992 Federal Register a draft policy statement on industry-sponsored scientific and educational activities and did not consider the draft policy statement's effect on the CVM assessment. We note that FDA is currently being sued over the issue of industry-sponsored continuing medical education. Because of this litigation and the continuing controversy over promotional activity occurring during continuing medical education meetings, we believe that CVM was correct in its assessment. Nonetheless, we believe that CVM accomplished its objective to stop further activity with the untitled letter it issued to Monsanto.

OIG Recommendation

1. Ensure that revisions are made to 21 CFR section 511.1(b)(8)(iv), in part, to address various pre-approval promotion activities sponsors can conduct in compliance with this Federal regulation and to increase the prominence of the regulation.

PHS Comment

We concur. The FDA's CVM is currently revising 21 CFR section 511. The current working draft regulation contains a separate subsection on promotion and distribution of investigational drugs. This will provide more prominence to the regulation of pre-approval promotion.

Although the specific final language is subject to change, this section currently acknowledges the purpose of the regulation as prohibiting commercialization of investigational

products rather than restricting the full exchange of scientific information and also provides examples. This is in line with CVM's May 1993 letter to Monsanto, similar to the equivalent regulation covering human drugs, and should substantially clarify the issue.

However, as noted above, FDA is already in litigation over the related issue of industry-sponsored continuing medical education. We believe that should the outcome of this litigation result in a significant limitation of the Agency's authority over the content of industry-sponsored scientific meetings, FDA would have to revisit this issue and possibly substantially revise the current draft regulations and guidelines.

OIG Recommendation

2. Develop criteria, formal staff guidelines, and policies, based on revisions to the Federal regulation, to be used for CVM review of potential pre-approval promotion activities.

PHS Comment

We concur. The FDA's CVM is currently drafting appropriate guidelines on promotion and advertising, subject to possible changes due to the results of the litigation described above.

Technical Comment

Page 7, paragraph 3. The draft report states that "Monsanto should have, but did not, clearly notify the company." This is incorrect. Instead of "Monsanto," it should be "CVM."