Memorandum

Date FEB 21 1992

From Richard P. Kusserow
Inspector General

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

To James 0. Mason, M.D., Dr. P.H.
Assistant Secretary
for Health

The attached final audit report presents the results of our audit of the Food and Drug Administration's (FDA) review of the new animal drug bovine somatotropin (bST). We conducted this audit at the request of Congressman John D. Conyers, Jr., Chairman, House Committee on Government Operations, who was concerned about: (1) inadequate research on the human safety of bST; (2) levels of bST in milk from cows treated with the drug: and (3) the possibility that FDA and Monsanto Agricultural Company (Monsanto), *one* of the drug *firms* developing bST, withheld, suppressed, and manipulated bST health-related data.

Our review focused on FDA's procedures in evaluating bST-related data, relevant scientific literature, the new animal drug application files for bST, and industry inspection reports. We found that research has been conducted to demonstrate both that bST is not harmful to humans, and that bST levels in milk are not higher in bST-treated cows than in non-treated cows. Our review also showed that FDA and Monsanto have appropriately withheld animal health data on bST, but FDA has publicly disclosed the data it reviewed on human food safety. Further, we found no evidence indicating that FDA or Monsanto engaged in manipulation or suppression of bST test data.

As to public statements made by FDA officials regarding the safety of bST and the likelihood of its approval, we conferred with the Department of Health and Human Services', Office of General Counsel, and concluded that such statements did not violate law or regulations. However, we believe that Federal Government officials should not publicly comment *on* the outcome of the *review* of a new animal drug. Therefore, we have recommended that the Commissioner of FDA develop policies and procedures on the type of public statements that can be

made regarding a new animal drug undergoing review. The FDA concurred with this recommendation and indicated it would expand such policies to make them FDA-wide covering all of its processes.

In reviewing the concerns about bST, we found no evidence that would lead us to question FDA's review of the human safety aspects of bST. However, since FDA has not completed its review of all bST-related data required for the new animal drug review process, particularly in the critical area of animal safety, it is not possible to determine the adequacy of the Agency's overall review at this time.

We would appreciate being advised within 60 days on the status of corrective action taken or planned on our recommendation. should you wish to discuss these issues, please contact me or your staff may contact Daniel W. Blades, Assistant Inspector General for Public Health Service Audits, at (301)443-3583.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

AUDIT OF ISSUES RELATED TO THE FOOD AND DRUG ADMINISTRATION REVIEW OF BOVINE SOMATOTROPIN

Richard P. Kusserow
INSPECTOR GENERAL

A-15-90-00046

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

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To James 0. Mason, M.D., Dr. P.H.
Assistant Secretary
for Health

This final report provides you the results of our audit of issues related to the Food and Drug Administration's (FDA) review of the yet-to-be approved new animal drug bovine somatotropin (bST). This audit was requested in May 1990 by Congressman John D. Conyers, Jr., Chairman, House Committee on Government Operations, who was concerned that:

-- little actual research exists on the human safety aspects of bST;

-- industry files indicate high levels of bST are found in the milk of bST-treated cows:

-- critical research information regarding health effects of bST on animals and humans has been withheld from public scrutiny by FDA and the Monsanto Agricultural Company (Monsanto), one of the firms developing bST; and

-- Monsanto and FDA have manipulated and suppressed animal health test data showing that bST-injected cows suffer low fertility rates, mastitis (inflammation of the udder), and other chronic defects.

Chairman Conyers raised these concerns after articles were published in the news media which appeared to contain conflicting information about bST. For example, some articles, specifically those published in Milkweed, a dairy farmers' magazine, used confidential data submitted to FDA in order to portray bST as having significant human and animal health risks. In contrast, other articles appearing in newspapers, trade magazines and scientific journals, contained statements made by the developers of bST and FDA officials implying that the yet-to-be approved drug was safe and nearing approval. Thus, the disparity in published accounts raised Chairman Conyers' concerns about the bST review process.

Our review disclosed that research was conducted to demonstrate that bST is not harmful to humans and that bST levels in milk are not higher in bST-treated cows than in non-treated cows. Our review also showed that Monsanto and FDA have appropriately withheld animal health data on bST, and that FDA lawfully and publicly disclosed data it reviewed on human food safety. Further, we found no evidence indicating that FDA or Monsanto engaged in manipulation or suppression of animal health test data.

However, during our audit work, we found that Monsanto had disseminated pre-approval promotional materials which claimed, without supporting scientific data, that bST was safe and effective prior to FDA approval of the drug. We disclosed our findings on this issue in a May 1991 report entitled, "Need for the Food and Drug Administration to Review Possible Improper Pre-Approval Promotional Activities." Because pre-approval promotion is contrary to Federal regulations, FDA agreed with our finding and completed a review of the pre-approval promotional materials of Monsanto and other groups and determined that "some type of regulatory action" was required to ensure that Monsanto, the other three sponsors, and the Animal Health Institute (a trade group representing manufacturers of veterinary drugs) conform to the regulations.

The Committee was also concerned about public statements made by FDA officials regarding the safety of bST and the likelihood of its approval. It appears that officials did not violate any Federal law or regulation by making such statements; however, we believe that some of the statements made could have given the appearance that FDA was prematurely predicting the outcome of the bST review process.

In reviewing Chairman Conyers' concerns about bST, we found no evidence that would lead us to question FDA's review of the human safety aspects of bST. However, since FDA has not completed its review of all bST-related data required for the new animal drug review process, particularly in the critical area of animal safety, it is not possible to determine the adequacy of the Agency's overall review at this time.

BACKGROUND

Since the early 1980's, FDA's Center for Veterinary Medicine (CVM), Division of Biometrics and Production Drugs, located in Rockville, Maryland, has been reviewing bST, also referred to as bovine growth hormone (bGH). Natural bST is a hormone produced by the pituitary gland of cows and helps to control

milk production. Using recombinant DNA technology', bST has been artificially produced for injection into dairy cows to increase their milk production. Four drug sponsors have filed applications with CVM to conduct investigations of and obtain commercial approval for their formulations of bST, which, according to CVM officials, is the first recombinantly derived product to be reviewed by CVM.

Section 512 of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. section 360b, requires any animal drug deemed a new drug to be approved by FDA as safe and effective before commercial marketing. Specific requirements for approval of new animal drug applications are set forth in section 512 of the Act and in 21 CFR 514. Federal regulations contained in sections 514.11 and 514.12 also require FDA to maintain the confidentiality of data contained in new animal drug application files undergoing Agency review.

For a new animal drug such as bST to receive FDA approval, the sponsor is required to demonstrate in its new animal drug application that the drug is: (1) safe for humans who consume food from animals treated with the drug: (2) safe for the treated animal: (3) effective: (4) safe to the environment: and (5) capable of being properly manufactured.

Early in the investigational stages of a new drug, a sponsor generally files with FDA an investigational new animal drug application to obtain authorization to conduct safety and effectiveness studies. At the conclusion of these studies, the sponsor then submits data from these studies in its new animal drug application. Section 512(j) of the Act and its implementing regulations enable FDA to authorize the marketing of edible products from animals used in investigational drug experiments. To obtain such authorization, the sponsor is required to show, among other things, that consumption of such products is not inconsistent with the public health. Based on the data provided by a sponsor, FDA determines a withdrawal period' which would be sufficient to prevent any harmful residues in the food products being consumed by the public during the investigational studies.

The CVM completed its review of the bST sponsors' human safety studies in 1986, determining that the food from bST-treated

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'A technology to synthesize in the laboratory substances such as biological chemicals or new life forms.

[2]The withdrawal period or the milk discard time is the interval between the time of the last administration of the drug and the time when the animal can be safely slaughtered for food or the milk can be safely consumed.

cows posed no risks to human health. It is continuing to review the sponsors' data on animal safety, efficacy, environmental safety, and manufacturing processes. Once these areas are evaluated, CVM can determine whether to approve bST for commercial availability.

The potential approval and expected commercialization of bST have been controversial, prompting considerable public debate and congressional inquiries regarding the drug's human and animal safety. To address these concerns, Senator Patrick J. Leahy, Chairman, Committee on Agriculture, Nutrition and Forestry, requested the National Institute; of Health (NIH) to sponsor a technology assessment conference on questions about the safety of bST.

The conference was held in December 1990. A panel of 13 non-NIH physicians and knowledgeable professionals was selected. The panel members were chosen because of their independence from the bST controversy and their experience in such areas as pediatric medicine, toxicology, veterinary medicine, and dairy and food science. The panel was charged with reviewing scientific data and weighing the evidence on the safety of milk and meat from bST-treated cows and bST's effect on the health of cows.

Based on the data it reviewed, the panel concluded that: (1) the composition and nutritional value of milk from bST-treated cows is essentially the same as milk from untreated cows; (2) milk and meat from bST-treated cows are as safe as those from untreated cows: and (3) bST administration does not appear to affect appreciably the general health of dairy cows, but the evidence did not permit a conclusion regarding its effect on the incidence of mastitis. The panel acknowledged that its assessment would not be the final statement on the issue because FDA continues to review bST data that were not available to the panel, particularly in the animal safety area.

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[3]The NIH holds such conferences, usually referred to as consensus development conferences, to examine topics related to emerging or established technologies which: (1) have public health importance: (2) have a controversy that could be clarified by the consensus approach: (3) have an adequately defined and available base of scientific information to answer previously posed questions and to resolve controversies: and (4) are amenable to clarification on technical grounds, not the impressions or value judgments of the conference panelists. An independent panel of non-NIH professionals is assembled for the conference in order to give balanced, objective, and knowledgeable attention to the topic.

OBJECTIVES, SCOPE, AND METHODOLOGY

The objective of this review was to respond to Chairman Conyers' concerns related to FDA's review of bST. To determine the adequacy of human health studies of bST and address the issue of bST levels in milk, we: (1) analyzed the laws, regulations, and guidelines pertaining to human safety reviews of animal drugs: (2) reviewed data from the studies conducted by each bST sponsor and scientific literature on the topic of bST's effect on humans: (3) interviewed FDA scientific staff in CVM and the Center for Food Safety and Applied Nutrition; and (4) attended the NIH technology assessment conference on bST.

To determine if critical research information had been improperly withheld from public scrutiny by FDA and Monsanto, we analyzed the laws and regulations regarding public disclosure of data contained in applications filed by new animal drug sponsors, and reviewed FDA legal documents filed in the U.S. courts pertaining to such disclosure.

To determine if manipulation or improper suppression of animal health effects had occurred, we: (1) interviewed CVM animal scientists and veterinarians who participated in the bST application review; (2) examined FDA field inspection reports of bST studies; (3) analyzed data files submitted by bST sponsors and summaries of those files compiled by FDA staff: (4) reviewed bST animal health literature published by Monsanto-sponsored researchers in scientific journals: and (5) consulted with the Department of Health and Human Services' (HHS), Office of General Counsel regarding the propriety of public statements made by Department officials on the issue of bST.

In August 1990, while reviewing Chairman Conyers' concerns, his staff brought to our attention a matter related to the propriety of Monsanto's pre-approval promotional marketing of bST. We reviewed this issue and disclosed our results in a May 1991 report, discussed further on page 11 of this report.

Our review was conducted at CVM offices in Rockville, Maryland, during the period from May 1990-March 1991, in accordance with generally accepted Government auditing standards.

RESEARCH CONCERNING THE HUMAN SAFETY OF BST

Chairman Conyers was concerned that little research existed on the human safety aspects of bST. Our review disclosed that research has been conducted to substantiate the Agency's determination that the milk and meat of bST-treated cows are

safe for human consumption. Clearly, the Office of Inspector General (OIG) can make no independent judgment as to the sufficiency of the scientific research. However, while critics continue to disagree about whether the research is sufficient, the NIH technology assessment conference panel concurred in FDA's determination. Following is a brief description of some of the research conducted on the issue of human safety of bST.

As part of the new animal drug application approval process, the drug sponsor must demonstrate to FDA that the food from animals treated with the drug is safe for humans. During the mid-1980's, each bST sponsor conducted rat feeding studies which demonstrated that bST would not be active when orally ingested, but rather would be degraded in the gastrointestinal tract like other proteins. The FDA itself also evaluated the human safety of bST by relying on data from experiments conducted in the 1950's showing that bST does not produce growth when injected into children afflicted with human dwarfism.

By 1986, FDA bad concluded, based on its evaluation of the four drug sponsors' human safety testing of bST and tests conducted by other experts, that the milk and meat from bST-treated cows were safe for human consumption and that no withdrawal period between treatment and consumption was required for investigational animals. Nevertheless, scientists within CVM continued to evaluate data that came to their attention regarding the human food safety aspects of bST.

One area of specific concern was bST's effects on the production of another growth factor, insulin-like growth factor-I (IGF-I), which is found in cow's milk. In 1988, information became available to CVM indicating that human IGF-I and bovine IGF-I are identical. This finding led to the question of whether bST administration in cows could cause higher levels of IGF-I in milk and, in turn, promote growth activity in humans. Thus, in May 1988, CVM asked the sponsors for IGF-I data.

According to CVM scientists who studied the human safety aspects of bST, the sponsors' studies demonstrated that IGF-I would not pose a problem for humans because: (1) IGF-I, like bST, is not orally active in rats: (2) the concentration of IGF-I in milk of bST-treated cows is within the normal physiological range found in human breast milk; and (3) IGF-I is rendered inactive under conditions used to process cow's milk for infant formula.

Certain bST critics have raised concern about pieces of the bST protein being absorbed from the digestive tract and having

biological activity. This has been cited with particular reference to newborns whose absorption of proteins may be greater than older children. The NIH panel, *however,* refuted this concern. The panel concluded that because bST and IGF-I are digested in the gastrointestinal tract and are not absorbed intact in the bloodstream, "they are not believed to have biological significance when ingested." Regarding infants, the panel stated that most are either breast fed or fed commercially prepared infant formulas that contain no more than trace amounts of growth hormone or IGF-I.

Some critics of bST have also questioned whether bST use will increase the incidence of disease in treated cows, thereby requiring greater use of drugs, whose residues may contaminate the milk. Contributing to this argument is a recent report issued by the General Accounting Office--"FDA Surveys Not Adequate to Demonstrate Safety of Milk Supply" (November 1990) --which states that FDA does not have test methods to detect and confirm many drugs believed to be used in dairy cows, and calls for a more thorough examination by FDA to identify the types and amounts of animal drug residues that may be contaminating milk.

The CVM officials responsible for reviewing bST are aware of this issue and told us they are currently analyzing the data provided by the bST sponsors to determine if bST is associated with increased disease rates or increased duration of diseases. They further explained that CVM and FDA's Center for Food Safety and Applied Nutrition are in the process of studying the issue of residue detection in milk. The CVM officials contend that the potential for animal drug residues to contaminate milk is a risk affecting all milk produced, not just milk from bST-treated cows.

BST LEVELS IN MILK IN BST-TREATED COWS VS. IN NON-TREATED COWS

Chairman Conyers was concerned that industry files indicate high levels of bST are found in the milk of bST-treated cows. The NIH conference addressed this issue and determined that "the concentration of bST in the milk of cows treated with the usual doses of rBST (bST) is no higher than the concentration in untreated cows."

During our audit, we found that there had been confusion about the level of bST in cows treated with bST. This confusion stemmed from a misunderstanding about data taken from Monsanto's confidential documents on file with FDA. These data were subsequently published in a dairy farmers' magazine using a title indicating that the data values were that of bST levels in milk produced by bST-treated cows. In reality,

however, documents we reviewed showed that the tables contained data on the level of bST in the cow's blood, not in their milk.

We discussed the issue of higher levels of bST in the blood of cows treated with bST with CVM officials. They explained that high producing cows, even those not treated with bST, tend to have higher levels of bST in their blood. Regarding the relationship between the cow's bST blood level and the milk it produces, two non-FDA related academic scientists writing on the safety of milk from bST-treated cows in the Journal of the American Medical Association, August 22/29, 1990 edition, stated that:

> "Following administration of bST to dairy cows, endogenous blood levels of bST (0 to 2.0ng/mL) may increase twofold to eightfold above background. Milk levels do not increase proportionally since no bST receptors exist on mammary gland cells to facilitate transfer of bST from blood to milk."

Thus, our review indicated that concerns over bST levels in milk were apparently generated by a mischaracterization of data on file at FDA. We were directed to research showing that while administration of bST increases a cow's bST blood level, it does not appear to increase the level of bST in the cow's milk. In our discussions about this issue, CVM officials maintained that even if bST levels in milk were to increase after bST administration, this would not pose a human safety concern because of the evidence indicating that bST is inactive in humans.

THE WITHHOLDING OF CRITICAL RESEARCH RESULTS FROM PUBLIC SCRUTINY

Chairman Conyers was concerned that critical research information regarding health effects on animals and humans has been withheld from public scrutiny by FDA and Monsanto. Our review disclosed that FDA and the bST sponsors have appropriately withheld data on bST from the public, even though some critics of bST review process contend that the results of bST tests should be publicized. The FDA is prohibited by Federal regulations from releasing any information from its investigational and new animal drug application files without the sponsor's permission if that information has not previously and lawfully been disclosed to the public; however, in this case, the Agency released some information with the permission of the bST sponsors. As to the drug sponsors' responsibility for disclosing data, they are required by regulation to submit all of the data from their studies to FDA as part of the application review process.

FDA Has Appropriately Withheld bST Data from Public Scrutiny

During the new animal drug review period, FDA is prohibited by Federal regulations contained in 21 CFR 514.11 and 514.12 from releasing any information regarding **a** sponsor's investigational new animal drug file or new animal drug application, even the fact that such documents have been submitted to the Agency.

According to FDA, the basis for these regulations is to protect an applicant company from unfair competition.[4] By disclosing the very existence of a new drug application a competitor could receive a marketing advantage. In terms of the information contained in the files, FDA seeks to protect the safety and effectiveness data because, if disclosed, this data could be used by competitors to obtain approval for their drugs. Therefore, by maintaining the confidentiality of each sponsor's research data, FDA believes the incentive remains for drug companies to conduct the often expensive and time-consuming research needed for approvals.

The FDA has made an attempt to present to the public information on the human safety aspects of bST--the one area in which there has been a determination as well as considerable public debate. Because of the public's concern about human safety, FDA has, with the permission of the bST sponsors, presented to the public information on its *reasons* for determining that food from bST-treated cows is safe. Further, in August 1990, at the request of Senator Patrick J. Leahy, two FDA staff scientists took the unprecedented step of publishing in a scientific journal the study results of the bST sponsors' human food safety tests. In contrast to the human safety area, the animal safety data is still under review and thus, the Agency **has** not made any final determination.

When a *new* animal drug application is approved, FDA at that stage publicly discloses information about the sponsor's studies. Specifically, at the time of the drug's approval, FDA prepares a "Freedom of Information Summary," which summarizes the results of all studies used to determine the target animal and human food safety and effectiveness of the drug product and essentially serves to explain the Agency's reasons for approving the drug.

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[4]The regulations implement 21 U.S.C. 331(j); 18 U.S.C. 1905, and 5 U.S.C. 552(b)(4).

bST Sponsors Have Appropriately Withheld Research Data from the Public

A sponsor of an investigational drug is required by 21 CFR 514.15 to submit to FDA all available records and reports from studies evaluating the safety and effectiveness of the drug, whether the studies are favorable or unfavorable. The sponsor, however, is under no legal obligation to release results of any studies to the public.

The sponsor may voluntarily choose, however, to release information about its investigational drug during the FDA review phase in efforts to exchange scientific information, such as in a scientific journal. With bST, the four sponsors have been relatively open about the existence of their applications and have published numerous articles in scientific journals pertaining to their bST research. Despite the openness of the bST sponsors, it is up to their discretion to select which data they wish to publicly disclose. The CVM officials emphasized that regardless of what data the sponsors disclose to the public, the final decision about a drug's safety and effectiveness resides with FDA, which reviews all the data submitted by the sponsor.

WE FOUND NO EVIDENCE THAT MONSANTO OR FDA ENGAGED IN DATA MANIPULATION OR SUPPRESSION

Chairman Conyers questioned whether Monsanto and FDA manipulated and suppressed animal health test data showing that bST-injected cows suffer low fertility rates, mastitis, and other chronic defects. The Committee staff indicated that they were specifically concerned if any of the following may have occurred:

-- Monsanto publishing only its positive bST data in scientific journals and promotional material, and FDA not disclosing to the public the actual data, including negative test data.

-- Monsanto misrepresenting its data submitted to FDA for review.

-- The FDA officials making public statements indicating that bST is safe and that approval is likely, even though animal safety studies show serious side effects.

As explained in detail below, our review disclosed no evidence that Monsanto or FDA had engaged in manipulation or suppression of animal health data. As stated previously, during the new animal drug review process, a sponsor has discretion in selecting which data it wants to publish in scientific journals: but it must submit all data to FDA, which

is required to keep that data confidential during the review. We found no indications that these **data were** misrepresented. We did find during our audit work that Monsanto had disseminated pre-approval promotional materials which claimed, without supporting scientific data, that bST was safe and effective prior to FDA approval of the drug. Regarding statements made by CVM officials to the public on the safety of bST and the likelihood of its approval, we conferred with HHS' Office of General Counsel and concluded that these statements did not violate Federal law or regulations. However, we believe that Agency officials should not publicly make predictions about a yet-to-be approved drug's safety and potential approval.

Propriety of Sponsors **Publishing bST Data**

With respect to sponsors publishing their bST data in scientific journals, CVM officials informed us that FDA does not have the authority to regulate the content of such journals, nor does it have policies and procedures in place to review such publications. Thus, it is possible that a sponsor could publish in a scientific journal a select portion of its data regarding its drug under review, even though FDA may have a full set of that data on file as part of the new animal drug review process. The CVM officials emphasized that the Agency does not make approval decisions based on articles published in scientific journals, but rather on the raw data submitted by the sponsor as part of the new animal drug application, which we determined during our audit contains data on both the positive and negative effects of bST on the animal's health.

In terms of whether FDA regulation of scientific journals was feasible, we conferred with the Office of General Counsel and determined that such regulation by FDA would raise substantial legal problems under the free speech clause of the Constitution.

The FDA does have authority, however, through Federal regulations contained in 21 CFR 511.1(b)(8)(iv), to regulate dissemination of promotional materials in which drug sponsors claim, without providing supporting scientific data, the safety and effectiveness of their investigational drug before FDA has made an approval decision on their new drug applications. We recently examined this very matter as part of a request by Chairman Conyers and determined that Monsanto and other drug sponsors had disseminated promotional materials containing claims that bST was safe and effective, without providing supporting scientific data, even before FDA had approved the product for commercial marketing.

In its February 1991 comments to our December 21, 1990 draft report regarding this matter, the Public Health Service (PHS)

agreed with our recommendations that FDA review the pre-approval promotional materials of Monsanto, the other three bST sponsors, and the Animal Health Institute, and take appropriate regulatory action.

Such action has included FDA sending a *letter* to Monsanto in January 1991 informing the company to conform to the regulation by immediately stopping the use of all materials that may lead persons to believe that bST is safe and effective. The letter required the company to respond to CVM's request within 15 days and stated that failure to comply with the request could incur additional regulatory action. After receipt of the letter, Monsanto and FDA communicated several times to clarify what information may be disseminated under the regulation. According to CVM, Monsanto agreed in March 1991 to abide by the pre-approval regulation and the interpretation of that regulation by FDA.

In February 1991, FDA sent similar letters to the other three bST sponsors and the Animal Health Institute. The CVM has received responses from each group; as of July 1991, CVM was still reviewing them to assess compliance with the regulation.

Monsanto bST Data Submitted to FDA for Review

Based on our review of Monsanto bST data on file with FDA and reports made by FDA's field inspectors of Monsanto's bST studies, it does not appear that the firm has misrepresented its bST data submitted to FDA as part of its new animal drug application.

Our review of Monsanto's new animal drug application file revealed that extensive data and discussions exist on both the positive and negative aspects of bST administration to dairy cows. These data were gathered both during Monsanto's animal safety tests, in which bST was given in high doses to identify health effects, and efficacy trials, in which bST was given in the proposed dose range to assess levels of milk production as well as health effects. The file also contained CVM's analyses of the application's contents, including letters from CVM to Monsanto indicating the areas where the firm's application was incomplete.

Monsanto's file included information concerning the potential animal health problems with bST in such areas as reproduction, mastitis, and injection site reaction. The CVM officials emphasized that CVM had not completed its review of the file. As such, it would not be possible for CVM to determine at this point how, for example, Monsanto has subsequently addressed the safety issues raised during earlier studies. Further, CVM must still determine whether the firm has adequately carried

out its scientific studies of bST--some studies could be rejected if CVM determines that they were not properly conducted or well-controlled. The CVM officials also explained that if a drug poses severe safety hazards, it will not be approved; however, less severe problems may be able to be overcome by approving a lower dose of the drug or properly describing the problems in the product's label.

We reviewed the results of FDA bioresearch inspections of 18 of the firm's bST clinical and nonclinical animal safety and efficacy studies. According to CVM officials, these are essentially all of Monsanto's studies which CVM will rely upon in making its safety and efficacy determination.

The CVM generally requests FDA field personnel to conduct bioresearch monitoring inspections for "pivotal" animal safety and efficacy research studies, which are the studies used to support the sponsors' new animal drug application. According to FDA's Compliance Program Guidance Manual, the purpose of inspections made of the clinical investigator is to: (1) assess the investigator's adherence to compliance program regulations and guidelines: (2) determine the validity of specific studies in support of products pending approval by FDA; and (3) determine that the rights and safety of subjects used in clinical studies have been properly protected. Bioresearch monitoring inspections made of nonclinical studies are to assure that the studies are conducted according to scientifically sound protocols.[5]

In our review of the 18 reports, the FDA inspectors found no evidence of Monsanto manipulating, suppressing, or otherwise misrepresenting study data.

Propriety of FDA Officials@
Statements about bST

Chairman Conyers has raised concern that CVM officials have made public statements regarding bST's safety and the timing for completing the review process. Such statements have appeared in, among other publications, the Food Chemical News, a trade publication.

For example, in the January 1, 1990, publication of the Food Chemical News, CVM's deputy director stated that "he would not disagree with industry predictions of an FDA decision on bovine somatotropin by the latter half of this year." The official cautioned that "the decision would not necessarily be approval but could be a call for more data," and added that

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'Protocols are detailed descriptions of the plans for a particular study.

"the data are not impossible to generate." The CVM official also called bST "one of the safest products we've ever administered" and described how the hormone affects the cow's lactation.

For a legal perspective on the propriety of such statements, we consulted with HHS' Office of General Counsel and concluded that the CVM officials had not violated any Federal laws or regulations by making such statements. Nonetheless, we interpreted these statements as essentially predicting the outcome of the new animal drug review process with respect to bST. As such, we are concerned that they could possibly result in the public perceiving FDA's review as lacking objectivity and integrity.

While recognizing that FDA officials have felt compelled to speak publicly about the bST controversy, particularly with respect to the human safety aspects, we do not believe officials should openly discuss areas undergoing review, such as animal safety, or make predictions about the review outcome. In our examination of this concern, a CVM official explained that regulations contained in 21 CFR 514.11 and 514.12 prevent FDA officials from disclosing the existence of a new animal drug application file. However, because the bST sponsors have already publicly acknowledged the existence of their files, FDA is allowed by these same regulations to publicly disclose their existence. These regulations do not, however, define the Agency officials' ability to make statements publicly predicting the timing and outcome of a drug review.

Beyond the regulations, we determined that FDA does not have written policies and procedures addressing what its officials can discuss once a drug file's existence has been publicly disclosed by the drug's sponsor. Thus, it appears that developing appropriate policies and procedures to govern public statements about drugs undergoing review could help the Agency avoid misleading perceptions and thereby help preserve the integrity of the process.

CONCLUSIONS AND RECOMMENDATION

The potential approval and eventual commercialization of bST have generated considerable debate regarding the drug's human and animal health safety. Because of the confusion regarding bST information printed in the media, we believe Chairman Conyers raised appropriate concerns, particularly since milk and meat are such important food products to the American people. In reviewing these concerns, however, we found no evidence that would lead us to question FDA's process for determining the human food safety of bST. Supporting FDA's determination is the NIH technology assessment conference,

which concluded that the milk and meat from bST-treated cows are as safe as those from untreated cows.

In terms of disclosure of data to the public, our review found that FDA and Monsanto have acted appropriately in their decisions as to what data may be disclosed regarding the human and animal safety of bST. Because FDA is constrained from fully disclosing data undergoing review, complete disclosure of bST data will not occur unless and until FDA approves the drug for commercial use. Given that FDA continues to review data on bST, we agree that the Agency should not allow the public to have full access to data regarding a yet-to-be approved product.

Chairman Conyers questioned whether FDA and Monsanto engaged in manipulation or suppression of animal health data. Our review did not disclose information substantiating such conduct. Our review indicated that Monsanto has provided FDA a full picture of its animal studies, with details on both the positive and negative aspects of bST administration, and that FDA is conducting its review of the animal health safety issues based on this information.

We also found that, during our audit, Monsanto had disseminated promotional materials containing claims that bST was safe and effective, without providing supporting scientific data, before FDA had approved the product for commercial marketing. Such pre-approval promotion is contrary to Federal regulation and could leave the impression that Monsanto has manipulated and/or suppressed its research data. According to PHS, FDA has reviewed the pre-approval promotional materials of Monsanto, the other three bST sponsors, and the Animal Health Institute, and determined that "some type of regulatory action" was required in each case to halt such promotion.

Statements made by CVM officials regarding the ultimate safety and review timeframes for bST could lead to public misperception about the new animal drug review process. Thus, we believe Agency officials should exercise a high degree of care in publicly discussing matters regarding new animal drug applications undergoing review. Accordingly, we recommend that you direct the Commissioner of FDA to:

-- develop policies and procedures on the type of public statements that can be made regarding a new animal drug undergoing review.

AGENCY COMMENTS AND OUR RESPONSE

In its December 17, 1991 reply to our draft report (see Appendix) the FDA agreed with our recommendation. In

addition, FDA believes that, based on the results of its own integrity review, this recommendation should be applied to all FDA review processes. One of the findings of the integrity review was that there are no written policies and procedures for FDA employees to follow on what constitutes permissible public statements for products undergoing review. The FDA believes that since this result of the integrity review is consistent with the finding in the OIG report and involves all of the FDA product review processes, an initiative should be undertaken to develop FDA-wide policies covering public statements regarding all products under FDA's review.

The FDA plans to form a task force to evaluate this problem and develop appropriate written policies and procedures for implementation. The FDA expects that this initiative will be completed by November 1992. The OIG agrees that such policies and procedures should apply to all products under FDA's review.

We would appreciate your comments *on* this final report within 60 days. Should you wish to discuss the issues presented in our report, please contact me or your staff may contact Daniel W. Blades, Assistant Inspector General for Public Health Service Audits, at (301)443-3583.

Appendix

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

DEC 17 1991

From Assistant Secretary for Health

Subject Office of Inspector General (OIG) Draft Report "Audit of Issues Related to the Food and Drug Administration (FDA) Review of Bovine Somatotropin"

To Inspector General, OS

Attached are the Public Health Service's comments on the subject OIG draft report. In addition to our comments on the report's findings and recommendation, **we offer a series of technical comments for your consideration.**

James O. Mason

James O. Mason, MMD., Dr P H.

Attachment

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OFFICE OF INSPECTOR
GENERAL
DEC 18 PM 4:33

IG	✓
PDIG	✓
DIG-AS	✓
DIG-EI	
DIG-01	✓
AIG-MP	
OGC/IG	
EXSEC	✓
DATE SENT	12/18

PUBLIC HEALTH SERVICE (PHS) COMMENTS ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT "AUDIT OF ISSUES RELATED TO THE FOOD AND DRUG ADMINISTRATION (FDA) REVIEW OF BOVINE SOMATOTROPIN," A-15-90-00046, OCTOBER 1991

General Comments

We are pleased with the report's finding that the concerns raised by Congressman John D. Conyers, Jr., were thoroughly reviewed and that there was no evidence that FDA engaged in manipulation or suppression of bovine somatotropin (bST) test data. We believe that OIG examined the relevant issues in a comprehensive and critical manner and reached conclusions that were clearly expressed and backed by rigorous analysis. We believe this review will ameliorate most of the concerns regarding the adequacy of FDA's review of bST.

OIG Recommendation

We recommend that the Assistant Secretary for Health direct the Commissioner of Food and Drugs to develop policies and procedures on the type of public statements that can be made regarding a new animal drug undergoing review.

PHS Comment

We agree with the recommendation. Based on the results from the Commissioner of Food and Drugs' integrity review, FDA believes that this recommendation should be applied to all of its review processes. One of the results of this integrity review was that there are no written policies and procedures for FDA employees to follow on what constitutes permissible public statements for products undergoing review. Since this result of the integrity review replicates the finding in the subject OIG report and involves all of the FDA product review processes, we believe that an initiative should be undertaken to develop FDA-wide policies covering public statements regarding all products under FDA's review.

In order to implement this initiative, FDA will form a task force to evaluate this problem and develop appropriate written policies and procedures for implementation. FDA expects that this initiative will be completed by November 1992.

Technical Comments

1. Page 1, second paragraph, third sentence

   We would like to clarify that the statement "approved drug was safe" should be viewed in the context that safety was meant only in the context of human food safety.

2. Page 2, first paragraph, second sentence

The word "but" should be replaced and the words "and that" be inserted before FDA and the words "lawfully and" inserted after FDA. In addition, please delete the word "has" before the words "publicly disclosed" and the word "the" before the word "data." The revised sentence should read as follows: "Our review also showed that Monsanto and FDA have appropriately withheld animal health data on bST, and that FDA lawfully and publicly disclosed data...".

3. Page 3, fourth paragraph, fourth sentence

To improve the clarity of this sentence, we suggest that a comma and the phrase "among other things," be placed after the word "show." Also, insert after the word "is" the words "not inconsistent," and delete the word "consistent." The revised sentence would read as follows: "To obtain such authorization, the sponsor is required to show, among other things, that consumption of such products is not inconsistent with the public health."

4. Page 6, second full paragraph, first sentence, fourth line

The word "withdrawal" should be inserted after the word "no", reading "...that no withdrawal period...".

5. Page 8, second full paragraph, third sentence

The phrase "without the sponsor's permission if that information has not previously and lawfully been disclosed to the public" should be inserted after the word "files" to improve the accuracy of the sentence. The sentence would then read as follows: "...new animal drug application files without the sponsor's permission if that information has not previously and lawfully been disclosed to the public;...".

6. Page 8, second full paragraph, last sentence

The clarity of the sentence will be improved with the following changes: the word "only" after "are" and before "required" should be deleted and the phrase "...release the results of..." should be replaced by "...submit all of the data from...". The revised sentence would read as follows: "As to the drug sponsors' responsibility for disclosing data, they are required by regulation to submit all of the data from their studies to FDA as part of the application review process."

7. Page 9, first paragraph, first sentence

After the first sentence, a footnote marker should be added and the following footnote be inserted to reference the statutory authorities that the regulations implement:

"The regulations implement 21 U.S.C. 331j, 18 U.S.C. 1905, and 5 U.S.C. 552(b)(4)."

8. Page 9, third paragraph, first sentence

The word "all" should be deleted so that it reads: ". . . . FDA at that stage publicly discloses information about...".

9. Page 9, third paragraph, first sentence

The word "investigational" should be deleted.

10. Page 9, third paragraph, second sentence

The words "target animal and human food" should be inserted before the word "safety" and the word *'effectiveness" replace the word "efficacy."

11. Page 10, first paragraph, third' sentence

The word "efficacy" should be replaced by the word "effectiveness."

12. Page 12, third full paragraph, second sentence

The word "generated" should be replaced by the word "gathered."