Animal & Veterinary

Report on the Food and Drug Administration's Review of the Safety of Recombinant Bovine Somatotropin

This report was updated on April 23, 2009 to clarify quantities of growth hormone found in milk and those used in the 1989 rat study.

INTRODUCTION

On November 5, 1993, following extensive review of the data to support the safety and effectiveness of the product, the Food and Drug Administration (FDA or Agency) approved the Monsanto Companys New Animal Drug Application for Posilac containing a recombinant bovine growth hormone (rbGH) (also known as recombinant bovine somatotropin, rbST, or Sometribove).

Growth hormone (GH) is a protein hormone produced in the pituitary gland of animals including humans and is essential for normal growth, development, and health maintenance. Approximately 60 years ago, it was discovered that injecting cows with GH extracted from cattle pituitary glands increased milk production. In the 1980s, it became technically possible and economically feasible to produce large quantities of bovine GH (bGH) using recombinant DNA processes. The Posilac product contains a recombinant bGH (rbGH) which is essentially the same as (pituitary derived) bGH.

In order to grant approval of Posilac, FDA determined, among other things, that food products from cows treated with rbGH are safe for consumption by humans. Vermont Public Interest Research Group and Rural Vermont have questioned the validity of this finding based on an analysis by reviewers at Health Canada (the Canadian counterpart of the FDA). This analysis, based in large part on a 90-day rat study, challenges the Agency's human health findings and argues that possible adverse health effects of Posilac were not addressed because long term toxicology studies to ascertain human health safety were not required by FDA or conducted by Monsanto.

FDA has completed a comprehensive, page by page audit of the human food safety sections of the investigational new animal drug file and master file supporting the rbGH approval. This audit examined all the studies used in determining the human food safety of rbGH, including the 90-day rat oral toxicity study and the report of the antibody response to oral rbGH upon which the Canadian reviewers relied. Upon determining that a review had not been performed of the antibody data during the course of the original review of the Monsanto application, these data were reviewed in their entirety. As set forth in detail below, FDA believes that the Canadian reviewers did not interpret the study results correctly and that there are no new scientific concerns regarding the safety of milk from cows treated with rbGH. The determination that long term studies were not necessary for assessing the safety of rbGH was based on studies which show that: bGH is biologically inactive in humans even if injected, rbGH is orally inactive, and bGH and rbGH are biologically indistinguishable.

ABSORPTION

When taken orally, proteins typically are broken down in the digestive process and are not absorbed into the body. To determine whether an rbGH product had biologically significant oral activity, the Agency required the drugs sponsor to perform short-term toxicology studies to assess whether biologically active rbGH was being absorbed into the body. Absorption of biologically active rbGH into the body could indicate a need for longer term studies to assess the possible impact on various body organs, particularly the liver. The study was conducted by orally administering rbGH to rats for 28 days at 100 times the daily dose administered to dairy cattle. FDA determined that there was no evidence for the absorption of biologically active rbGH following oral administration because there were no dose-related trends associated with oral administration of rbGH to rats for 28 days.

The Canadian analysis takes issue with the Agency's findings regarding a 90-day rat oral toxicity study performed by Monsanto to fulfill a requirement of the European Union (EU) for rbGH approval. The study was conducted by a Searle laboratory of Monsanto and submitted to FDA pursuant to FDA's requirement that all relevant safety information for an investigational new animal drug be included in the sponsor's application. The FDA reviewed the study in 1989, except as noted below, and it was determined that there were no observed effects from oral administration at any dose. In this study, there was evidence that oral administration of rbGH produced an antibody response; however, such response was consistent with that produced by a number of food proteins and is not necessarily an indication of absorption of intact rbGH.

As rbGH produces significant biological effects when injected into rats, this study supported the inability of rbGH to cause significant biological effects following oral administration even at doses 50 times greater than the injected dose.

The report of the 90-day rat oral toxicity study included discussion of a satellite study group of rats. This satellite study was conducted to investigate the antibody response to rbGH as an indirect measure of the possible absorption of rbGH from the rat gastrointestinal tract. This satellite study was not reviewed when originally submitted.(1) Once this oversight was detected, the Agency immediately undertook the review of the data.

FDA's review of the antibody response study "Determination of Sometribove immunoglobulin in rat serum" was completed on November 30, 1998. The study showed:

1. Six out of 30 rats receiving 5 mg (10^{-3} grams)/kg/day oral rbGH, and 9 out of 30 rats receiving 50 mg/kg/day produced antibodies, while there was no measurable response at 0.5 mg/kg/day (500 µg (10^{-6} grams)/kg/day). Thus, at high doses these data appear to show some systemic anti-rbGH response to the oral administration of rbGH to rats.
2. The methodology used in this study, however, was inadequate to determine the systemic bioavailability of oral rbGH. Immune cells throughout the body, including cells in the gastrointestinal tract and in the systemic circulation, produce antibodies. Antibodies produced in the gastrointestinal tract, however, can travel from the gastrointestinal tract to the systemic circulation. Thus the presence of antibodies in the systemic circulation is not proof of systemic absorption of rbGH from the gastrointestinal tract.(2)
3. The level of antibodies present in rat plasma is relatively low and would not be expected to have any adverse effect on the host.
4. It may be calculated, based upon consumption of 1.5 liter of milk per day, by a 10 kg child, with a concentration of approximately 5 micrograms (µg: 10^{-6}) rbST per liter of milk(3), that children are exposed to 7.5 µg/kg/day. This concentration is several hundred fold below the lowest dose that elicited antibody production in the submitted study (0.5 mg/kg/day). Thus, the daily amount of rbGH needed to result in systemic antibody levels is orders of magnitude above that which could reasonably be expected to be consumed on a daily basis.(4)

It is noted that there were no dose-related effects on body weight or organ weight found in either the 90-day oral exposure study or the pivotal 28-day oral exposure study in rats, demonstrating a lack of biological activity.

In addition, a study published in 1988 by Seaman et al.(5) demonstrated that orally administered doses of up to 40 mg/kg/day of bovine somatotropin had no effect on weight gain (while such effects were observed following injection of the drug). This study demonstrated a dose-dependent increased weight gain in hypophysectomized rats administered bovine somatotropin at doses of 0.15, 0.30, and 0.60 mg/kg/day for up to 9 days by subcutaneous injection. Oral administration of bovine somatotropin at doses up to 40 mg/kg/day had no effect on body weight gain in this sensitive bioassay. Subcutaneous administration of bovine somatotropin to hypophysectomized rats resulted in a modest increase in serum antibodies to rbGH by the end of the study (day 9) coupled with measurable plasma levels of bovine somatotropin by radioimmunoassay. Oral administration resulted in no detectable levels of bovine somatotropin in the blood while there was a detectable production of antibodies. Seaman et al conclude that this study does not provide evidence for the absorption of intact somatotropin following oral administration as there was no effect on weight gain nor could somatotropin be measured by the analytical method. The authors conclude that the

antibody response was most likely directed toward recognizable fragments of the parent protein molecule rather than intact bovine somatotropin. As to the question of whether the antibody response itself might be considered an adverse effect, the authors cite several reports showing that the vast majority of healthy infants and 15 - 30% of adults have antibodies to various dietary proteins, especially milk-derived proteins. The FDA reviewed the study published by Seamanet al. and generally agreed with the reported conclusions.

FDA believes that the available data confirm that biologically significant amounts of rbGH are not absorbed in humans following the consumption of milk from cows treated with rbGH. Oral toxicity studies of longer duration are not necessary because rbGH at dietary levels found in the milk of rbGH-treated cows is not significantly biologically available.

THYROID CYSTS and PROSTATE INFILTRATION

In addition to the antibody results, concern has been raised that the 90-day rat study suggested that rbGH caused the rats to develop thyroid cysts and an infiltration of cells into the prostate. It is argued that such results, if true, would be evidence of absorption of rbGH and possible harmful effects.

An examination of the individual animal reports for gross and histopathological findings revealed thyroid cysts in all treatment groups, including the positive and negative controls.(6) Neither frequency nor severity of these cysts appeared to be related to rbGH administration by either the oral or subcutaneous routes, at any dose, in either gender. Thyroid cysts are enlarged thyroid follicles, and are not related to cancer formation.

A similar examination also was made for the prostate observations. The mononuclear cell infiltration observed is an indication of mild inflammation, and again, is not related to cancer formation. The prostate and accessory sex glands are frequent sites of inflammatory changes in male rats. These changes are common in older rats, but they also occur in young adult rats. Although there appears to be a dose-related increase in the number of rats showing mononuclear cell infiltration following oral administration, there was no difference between the negative and positive control groups. If the prostatic changes were induced by rbGH, it would be expected that the frequency and severity of changes would be significantly greater in the positive versus the negative control group. Therefore, as with the thyroid cysts, these observations do not appear to be related to treatment of the rats with rbGH. Neither the thyroid nor prostate changes provide any evidence of an observable effect of rbGH in the rat and do not provide evidence of absorption.

IGF-I

The Canadian report indicates that milk from rbGH-treated cows contains significantly elevated levels of insulin-like growth factor I (IGF-I) in milk, and presents human health safety concerns. IGF-I is a protein normally found in all humans, and is not intrinsically harmful. IGF-I is necessary for normal growth, development, and health maintenance. Circulating plasma levels of the hormone increase from birth to late puberty and subsequently decline in adults to approximately 100 ng (10-9 grams)/ml (range = 42 - 308 ng/ml for men and women >23 yrs). IGF-1 is structurally similar to insulin and, like insulin, is not biological effective following oral administration.

The safety of IGF-I in milk was thoroughly considered by FDA in its review of the Posilac application. Some early studies suggested that treatment of dairy cows with rbGH produced a slight, but statistically significant, increase in the average milk IGF-I concentration. FDA determined that this modest increase in milk IGF-I concentration was not a human food safety concern because it was less than the natural variation in milk IGF-I levels observed during lactation and was less than the fluctuation observed in milk from treated and control cows prior to rbGH administration.

Since making that analysis, however, FDA has received and reviewed several more comprehensive studies designed to ascertain the effect of rbGH treatment on milk IGF-I levels. These studies have demonstrated that the levels of IGF-I found in milk from treated cows are within the range of those normally found in milk from untreated cows. In 1993, the JECFA Committee concluded, "the most definitive and comprehensive studies demonstrate that IGF-I concentrations [in milk] are not altered after rbGH treatment". The 1998 JECFA Committee report summarized a study showing no significant difference in commercially available milk labeled as coming from non-rbGH treated cows and milk from cows presumed to be treated with rbGH but not labeled as to treatment.

A recent study(7) has been published on the association between prostate cancer and IGF-I. This study showed a positive correlation between the level of IGF-I in plasma and the increased risk of prostate cancer. Although the mechanism responsible for induction of cancer has not been characterized fully, it is clear that IGF-I is not the causative agent.

FDA has examined the literature and finds no definitive evidence of any direct link between IGF-I and breast cancer. Some authors have hypothesized a link, whereas others have expressed that while IGF-I is one of several growth factors and hormones that can contribute to an increase in cell numbers of many cell types invitro, no one factor is responsible for changing normal cells into cancerous cells. Furthermore, FDA has been advised that there is no substantive evidence that IGF-I causes normal breast cells to become cancerous.(8)

In evaluating the potential for human health risk from a natural component of the body, one can examine the effect of an increased exposure to IGF-I by employing several assumptions (i.e., IGF-I levels in milk from rbGH-treated cows are increased from 4 ng/ml to 6 ng/ml, all of the IGF-I in milk is absorbed into the body, and absorbed IGF-I is confined to the vascular compartment). Assuming 5000 ml blood plasma volume in a 60 kg person and assuming this person consumes 1.5 liters of milk containing 9000 ng IGF-I from rbGH-treated cows (as opposed to 6000 ng IGF-I in milk from untreated cows), the maximum increase in blood IGF-I would be less than 2 ng/ml of which only one-third could be attributed to the use of rbGH. This minute increase would dilute into the endogenous pool of circulating IGF-I. IGF-I entering the circulation is rapidly bound to serum binding proteins which attenuate the biological activity.(9)

It bears repeating that the assumptions that milk levels of IGF-I are increased following treatment with rbGH and that biologically active IGF-I is absorbed into the body are not supported by the main body of science. Careful analysis of the published literature fails to provide compelling evidence that milk from rbGH-treated cows contains increased levels of IGF-1 compared to milk from untreated cows. Despite recent studies that demonstrate that milk proteins protect IGF-I from digestion, the vast majority of the published work indicates that very little IGF-I is absorbed following ingestion. The most recent 1998 review by the JECFA concluded that, "the concentration of IGF-I in milk from rbGH-treated cows is orders of magnitude lower than the physiological amounts produced in the gastrointestinal tract and other parts of the body. Thus, the concentration of IGF-I would not increase either locally in the gastrointestinal tract or systemically, and the potential for IGF-I to promote tumor growth would not increase when milk from rbGH-treated cows was consumed; there is thus no appreciable risk for consumers."

EFFECT OF rbGH ON INFANTS AND CHILDREN

Strong concerns over the potential risk to infants and children of milk containing rbGH were expressed by Vermont Public Interest Group and Rural Vermont but no specific issues were raised to substantiate this concern. The FDA considers the impact on high-risk populations in assessing the safety of new animal drugs. For rbGH in particular, issues related to levels of IGF-I in infant formula were carefully examined by FDA. Other concerns, including the hypothetical development of insulin-dependent diabetes mellitus following the consumption of milk from rbGH-treated cows, have been reviewed by the Agency as well as other national and international scientists. To date, all of these reviews have concluded that consumption by infants and children of milk and edible products from rbGH-treated cows is safe.

MASTITIS

An August 6, 1992 General Accounting Office (GAO) report found that FDA's review of rbGH had met all established guidelines and that bovine growth hormone did not appear to represent a direct human health risk. However, because rbGH-treated cows tended to have a small but significantly greater incidence of mastitis, GAO recommended that the degree to which antibiotics must be used to treat mastitis should be evaluated in rbGH-treated cows with respect to human food safety. In response to GAO's recommendation, FDA's Center for Veterinary Medicine convened its Veterinary Medicine Advisory Committee and other expert consultants for an open public hearing on March 31, 1993. The Committee concluded that, while rbGH treatment might cause a statistically significant increase in mastitis, the human health risk posed by the possible increased use of antibiotics to treat the mastitis was insignificant. Again, the recent JECFA report addressed the issue of antibiotic use associated with rbGH use. The Committee concluded "The use of rbGH would not result in a higher risk to human health due to the use of antibiotics to

treat mastitis and that the increased potential for drug residues in milk could be managed by practices currently in use within the dairy industry and by following directions for use."

EXTERNAL REVIEWS HAVE CONFIRMED VALIDITY OF FDA REVIEW

The FDA's review of rbGH has been scrutinized by both the Department of Health and Human Services' Office of Inspector General (OIG) and by GAO, as well as by JECFA. On February21, 1992, the OIG announced that an audit of issues related to FDA's review of rbGH found no evidence to question FDA's process for determining the human food safety of rbGH. The OIG found that sufficient research had been conducted to substantiate the safety of the milk and meat of rbGH-treated cows for human consumption. In addition, the OIG found no evidence that indicated that FDA or Monsanto engaged in manipulation or suppression of animal health test data. As noted above, the August 6, 1992 GAO report found that FDA's review of rbGH had met all established guidelines and concluded that bovine growth hormone did not pose a risk for human consumption. In its reviews, JECFA also came to the conclusion that rbGH can be used without any appreciable risk to the health of consumers.

FOI SUMMARY REQUIRED TO INCLUDE ONLY PIVOTAL STUDIES

FDA's Center for Veterinary Medicine (CVM) has distributed "Freedom of Information Summary Guidelines" (Guideline #16) to assist sponsors of New Animal Drug Applications (NADAs) in preparing these summaries and to assist the Center in reviewing the summaries and preparing the "Agency Conclusions" section. This guideline, which was last revised on May 10, 1985, states that when approval of an original or supplemental NADA is published in the Federal Register, a summary of the safety and effectiveness information submitted to support the approval of the application (pivotal studies) is publicly released by the FDA.

The 90-day rat study was not included in the Freedom of Information (FOI) study because it was not a pivotal study. The human food safety section of the FOI summary (p. 119) does refer to the Juskevich and Guyer article in Science, "Bovine growth hormone: human food safety evaluation," (249:875-884, 1990). This article discusses the 90-day rat study (pp. 877-878).

CVM-1

1 Although FDA did not review the antibody data when originally submitted, FDA scientists participated in the discussion of antibody data at the 1992 Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives (JECFA) meeting. The JECFA report states, "Serum somatotropin and rbST antibody production results indicate that orally ingested bST was not absorbed intact from the rat gut at the dose levels tested. Antibody titers slightly higher than background were present in several of the orally-treated rats, but rbST was not detected by RIA [radioimmunoassay]. These data suggest that the immune system has access to an antigenic portion of rbST (Seaman & Skinner, 1986). Formation of antibodies to dietary proteins is a normal response (Bahna & Heiner, 1980: Hammond et al., 1991)." WHO Food Additive Series 31 (1993) Bovine Somatotropins (A Toxicological Evaluation of Certain Veterinary Drug Residues in Food) Annex 1 104:149-165.

2 National Institutes of Health, (1984) Fate of Ingested Antigens in the Intestinal Tract. In Adverse Reactions to Foods. U.S. Dept. of Health and Human Services, NIH Publication number 84-2442, 27-42.

3 Groenewegen, P.P, McBride, B.W., Burton, J.H., and T.H. Elsasser. 1990. Bioactivity of milk from bST-treated cows. J. Nutr. 120: 514-520.

4 This conclusion is consistent with the conclusion of the European Union's Committee on Veterinary Medicinal Products that established an oral no-observable-effect-level of 0.5 mg/kg rbGH.

5 William J. Seaman, John L. Nappier, Richard F. Olsen, Melody D. Charlton, Paul J. Skinner, Royal J. Weaver, Gregory A. Hoffman, (1988) The Lack of a Growth-Promoting Effect of Orally Administered Bovine Somatotropin in the Rat Body-Weight-Gain Bioassay. Fundamental and Applied Toxicology, 10:287-294.

6 Rats in the positive control group received rbGH by injection. Rats in the negative control group received no rbGH.

7 June M. Chan, Meir J. Stampfer, Edward Giovannucci, Peter H. Gann, Jing Ma, Peter Wilkinson, Charles H. Hennekens, Michael Pollack, (1998) Plasma Insulin-like Growth Factor-I and Prostrate Cancer Risk: A Prospective Study. Science, 279:536-566.

8 Taken from a letter from Dennis M. Bier, M.D., Professor of Pediatrics and Director, Children's Nutrition Research Center, College of Medicine, Baylor University, to David A. Kessler, M.D., Commissioner, Food and Drug Administration, February 25, 1994.

9 Louis E. Underwood and Judson J. Van Wyk, (1992) Normal and Aberrant Growth. In Williams Textbook of Endocrinology, Jean D. Wilson and Daniel W. Foster, eds. WB Saunders Co., Philadelphia, 1079-1138.

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