



Food and Drug Administration  
Rockville MD 20857

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- Andrew Kimbrell, Executive Director  
Joseph Mendelson, III, Legal Director  
Center for Food Safety  
c/o International Center for Technology Assessment  
310 D Street, N.E.  
Washington, DC 20002

Re: Docket No. 98P-1194

Dear Sirs:

This is the final response to your Citizen Petition dated December 15, 1998 and its January 15, 1999 amendment. The petition concerns Posilac®, a recombinant bovine growth hormone (rbGH) product (also known as rBGH, sometribove, recombinant bovine somatotropin and rbST), sponsored by the Monsanto Corporation (Monsanto) and approved for marketing by the Food and Drug Administration (FDA). (Posilac® is a registered trademark for Monsanto's rbGH product with the U.S. Patent and Trademark Office.) The FDA approved Posilac on November 5, 1993, following extensive review of the data, which support the safety and effectiveness of the product.

Prior to commercial distribution of any new animal drug for use in food-producing animals, a sponsor must prove its product is safe and effective when used as described in the proposed labeling of the drug. Effectiveness simply means that the product does what the labeling claims. Safety routinely covers the safety of the food products to humans and safety to the target animals. In addition to these requirements, the sponsor must prove that they can consistently manufacture the drug to a specific purity, potency and quality. The FDA's Freedom of Information (FOI) Summary for Posilac (NADA 140-872) summarizes the basis for FDA's conclusions regarding the safety and effectiveness of the drug and is available to the public.

Your petition was filed with the agency on December 16, 1998. You requested the following actions:

1. That FDA "immediately suspend the approval of the new animal drug application for Posilac-recombinant bovine growth hormone (rBGH)";

98P-1194

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2. That FDA "immediately publish a Notice of Opportunity for an Evidentiary Hearing concerning "new evidence" related to the new animal drug application approval of Posilac (rBGH) in the Federal Register";
3. That FDA, "upon completion of the hearing, issue an order withdrawing the approval of the new animal drug application for Posilac (rBGH)"; and
4. That FDA "revoke all regulations associated with the approval of Posilac (rBGH) including those found at 21 C.F.R. 522.2112."

The basis for your petition is that there is new evidence not previously before FDA which "suggests that oral consumption of rBGH may trigger human health risks." The new evidence to which you refer is an interim report from Health Canada's rBST Internal Review Team that was issued on April 21, 1998. (The Canadian counterpart to the U.S. FDA is Health Canada.) We highlight, however, that Health Canada's final report on rbGH issued on January 15, 1999, "found no significant risk to human safety through ingestion of products from rbST-injected animals" (News Release summary).

You amended your petition on January 15, 1999. Your amendment included as an additional basis for the actions requested in your original petition that "use of Posilac (rBGH) presents an imminent hazard to the health of animals." The basis for this allegation is another report also released on January 15, 1999, by the Canadian Veterinary Medical Association (CVMA) at the request of Health Canada. Health Canada requested that the CVMA review the issue of animal safety and effectiveness of rbGH products.

(A summary of Health Canada's regulatory decisions regarding the use of rbGH is available on line at <http://www.hc-sc.gc.ca/english/archives/rbst>. There are two separate final reports for evaluation: one on human health (by the Royal College of Physicians and Surgeons of Canada) and another on animal health (by the CVMA). These formal reports were requested by Health Canada and serve as the basis for Health Canada's decision regarding rbGH. Additionally, and again available on-line, there is a formal News Release summary (issued on January 14, 1999) combining the conclusions of the two final reports. Within your petition, only preliminary position papers (such as the Internal Review Team's report) and subsections of the final report are referenced. In constructing FDA's response to this petition, we have chosen to quote from the final reports or the formal News Release summary.)

As amended, your petition raises two primary areas of concern, human food safety of products derived from animals treated with Posilac and the safety to animals treated with Posilac. The specific issues that you raise with regard to Posilac are:

- 1) That there is evidence of oral absorption of rbGH;
- 2) That IGF-I can survive digestion;
- 3) That there is a possible relationship between IGF-I and cancer;
- 4) That there is a possible relationship between rbGH and BSE;

- 5) That the FDA failed to evaluate the human health risks associated with rbGH;
- 6) That animals injected with rbGH suffer a significant increase in mastitis;
- 7) That animals injected with rbGH suffer a significant increase in lameness; and
- 8) That animals injected with rbGH suffer a significant increase in infertility.

You assert that these issues warrant the immediate suspension of the new animal drug approval for Posilac as well as the publication of a notice of opportunity for hearing proposing withdrawal of approval of the product, holding an evidentiary hearing, withdrawing the approval (apparently without regard to what decision might be rendered based on the hearing) and revoking any regulations that reflect the approval of Posilac.

We have thoroughly reviewed the issues you raised in your petition. We believe that the arguments presented in your petition do not demonstrate human food or target animal safety issues that would provide a basis for initiating proceedings to withdraw the approval of Posilac. Therefore, your petition requesting withdrawal of the approval of Posilac is denied. We note that we do not have the authority to suspend a new animal drug approval based on imminent hazard. Under section 512(e)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), only the Secretary (or in her absence the officer acting as Secretary) may suspend approval of a new animal drug application based on imminent hazard. We believe, however, that since the issues you raised do not support withdrawal of the new animal drug application for Posilac, those issues also would not support a suspension of the application based on imminent hazard by the Secretary.

## **I. Human Food Safety**

Within your original petition, you present four predominant concerns regarding the human food safety of products derived from animals supplemented with rbGH. A fifth concern addresses FDA's evaluation of rbGH on a more procedural level. To support these concerns, you have included two attachments from Health Canada and a third attachment written for presentation at an international meeting on rbGH. We note that several issues mentioned in the petition's attachments, and referred to directly within the petition, have been previously addressed by FDA in the "Report on the Food and Drug Administration's Review of the Safety of Recombinant Bovine Somatotropin," which was issued shortly after, but independent of, the filing of your petition. (This report will be referred to within this response as FDA's Report.) A copy of this report, published on February 10, 1999, is available on-line at <http://www.fda.gov/cvm/fda/infores/other/RBRPTFNL.htm>.

### **1) The possibility of oral absorption of rbGH.**

Your petition expressed concern about the absorption of rbGH. The following is excerpted from your petition:

"The Health Canada data review found evidence that laboratory rats orally fed high dose of rbGH were absorbing the substance. More specifically, the report details that a Monsanto ninety (90) day rat feeding study actually found that between twenty [percent] (20%) and thirty [percent] (30%) of the rats in the study developed primary antibody response to rbGH - an indication that orally administered rbGH was absorbed into the blood stream and it produced a distinct immunological effect." Page 12, 1<sup>st</sup> full paragraph.

In the same portion of the petition, you challenge the FDA's toxicological conclusions regarding rbGH's safety. Quoting from your second Attachment to the petition, Health Canada's Internal rBST Review Team's meeting minutes:

" ... there were cysts in the thyroid of male rats in the high dose group, and some increased mononuclear infiltration in the prostate of high dose males." Page 3, 6<sup>th</sup> full paragraph.

First, we would like to point out that protein consumption is crucial to the human diet. Like most dietary proteins, rbGH is degraded by digestive enzymes in the gastrointestinal tract. *In vitro* studies on the metabolism of rbGH demonstrate that digestive enzymes readily cleave the molecule (Heiman et al., 1989). The progressive cleavage of peptide bonds results in the loss of biological activity because both the C- and N-termini and appropriate tertiary structure are required for receptor binding. *In vivo* studies confirm that proteolytic fragments of rbGH produced by digestive enzyme cleavage have no biological activity (Hammond et al., 1990). In fact, one of the most common techniques for studying the primary structure of proteins is trypsin cleavage. In this technique, the protein molecule is treated with a proteolytic enzyme commonly found in the human digestive tract, trypsin, and the peptide bonds of the protein are broken down such that the amino acid sequence may be determined.

We disagree with the conclusions you have drawn with respect to the "Three-Month (90-day) Oral Toxicity Study of Somatotribove in the Rat." (Your petition includes a discussion of this study in Attachment 1's Appendix VI.) This is a study of complex design and the FDA welcomes the opportunity to clarify both the design of the study and its interpretation. We note that FDA's Report contained a review of this study. The following discussion will address the full study.

In this study from Monsanto, conducted by Richard, Odaglia and Deslex, Charles River VAF rats (30 per sex/treatment group) were administered rbGH by oral gavage (0, 0.1, 0.5, 5 and 50 mg/kg bw) or subcutaneous injection (1 mg/kg bw) once daily for 90 days. Clinical observations, morbidity, mortality, body weights, and feed consumption were recorded for all rats. Upon cessation of drug treatment, 15 rats/sex/treatment group were necropsied to determine toxicology endpoints, including ophthalmology, hematology, clinical chemistry, urinalysis, pathology and histopathology.

The remaining 15 rats/sex/treatment group were used for the blood collection/reversibility groups. Blood samples were obtained from all of these rats prior to drug administration. Of these animals, blood samples were collected from 10 rats/sex/treatment group during week 7 of treatment and at week 14 (upon cessation of drug treatment). These rats were then removed from the study and destroyed without necropsy. The remaining 5 rats/sex/treatment group (the reversibility group) was also bled at week 14, and then on study week 28 (recovery week 14). At study week 28, following the collection of blood and recording of body weight and feed consumption, these animals were destroyed without necropsy.

Data collected for the 10 rats/sex/treatment group that made up the blood collection experimental group were limited to serum rbGH antibody concentration. Data collected for the 5 rats/sex/treatment group that made up the reversibility experimental group were limited to body weights, body weight change, feed consumption, and serum rbGH antibody concentration.

Thyroid cysts were observed in the gross and histopathological examinations in all treatment groups, including the positive and negative control groups. Neither the frequency nor severity of the cysts was attributable to rbGH treatment. Similarly, prostatitis was observed in animals from all treatment groups including the positive and negative control groups and again this was not attributable to rbGH treatment. Given that thyroid cysts and prostatitis were observed in both the treatment groups and the control groups, these observations cannot be attributed to rbGH treatment. No adverse effects of rbGH were observed in any animals of the toxicology group.

There were no statistically or biologically significant effects of daily oral rbGH in clinical observations, body weights, body weight change or feed consumption, either during treatment or during the recovery phases. Daily administration of subcutaneous rbGH significantly increased body weights, body weight change, organ weights, and feed consumption in the toxicology experimental group. However, body weights, body weight change, and feed consumption following subcutaneous administration returned to the "base-line" levels found in the control group animal values over the course of the recovery period.

Administration of subcutaneous or oral rbGH resulted in a significant increase in plasma antibody concentration. One out of 30 rats (male and female) receiving 0.1 mg/kg bw oral rbGH per day, 6/30 rats receiving 5 mg/kg bw, and 9/30 rats receiving 50 mg/kg bw per day had a measurable plasma antibody response following 90 days of continuous oral treatment. Twenty-seven out of 28 rats showed a significant antibody response following 90 days of subcutaneous rbGH injection (1 mg/kg bw). Fourteen weeks after cessation of rbGH administration, 9/10 rats of the subcutaneous rbGH treatment group, and 2/10 rats of the 50 mg/kg bw oral rbGH treatment group had measurable titers. However, the immunological assay could not distinguish between an antibody response to intact rbGH or fragments of rbGH. It was also not possible to distinguish between antibodies produced in response to absorbed rbGH or gastrointestinal rbGH. Thus, the antibody response does not establish that rbGH is absorbed intact.

To address your concern regarding the development of a "primary antibody response to rbGH" (Page 12, 1<sup>st</sup> full paragraph), we note that an immunologic response to exogenous proteins is

normal. There is a considerable body of public literature demonstrating that oral administration of large amounts of food proteins (e.g., bovine milk caseins, lactoglobulins, lactalbumins, egg white protein) to laboratory animals and to humans can induce the formation of circulating antibodies (Bahna & Heiner, 1978; Rothberg et. al., 1967). Indeed, most children and some adults carry antibodies to bovine milk proteins as well as a multitude of other dietary proteins. Thus, the detection of rbGH antibodies in rats orally administered large amounts of rbGH is a normal physiologic response.

In conclusion, we refer you to Attachment 1 of your original petition (the Gaps Analysis Report by Health Canada) in which the final paragraph states (page 33, just before the tabulated information): "Humans will be exposed to much smaller amounts of sometribove, which based on the rat data, will be far below a level which can generate an immunologic response."

## **2) The possibility of IGF-I surviving digestion.**

Your petition expressed concern about the oral activity and absorption of IGF-I. Quoting from your petition: "New evidence contradicts the FDA's previous findings that IGF-I does not survive digestion." This new evidence includes oral rat feeding studies that putatively demonstrate IGF-I survives digestion when in the presence of milk proteins and that upon absorption the IGF-I was physiologically active in rats. As support you provide Attachment 3 and some journal articles. Attachment 3 to your petition, by Hansen et al., ("Potential Public Health Impacts of the Use of Recombinant Bovine Somatotropin in Dairy Production") was prepared for a Scientific Review by the World Health Organization/Food and Agriculture Organization's Joint Expert Committee on Food Additives (JECFA). Quoting from the abstract of Attachment 3:

"The weight of evidence clearly indicates that levels of hormone Insulin-like Growth Factor I (IGF-I) are significantly elevated in milk from rbST-treated cows; with widespread use of rbST, average IGF-I levels in milk could be expected to rise. Several recent studies have demonstrated that IGF-I, in the presence of the milk protein casein and certain other protective factors, largely survives digestion in the stomach and passes into the intestines."

One of your main areas of concern is that IGF-I in milk will result in IGF-I levels that are elevated in humans after they consume milk from cows supplemented with rbGH. The FDA has previously maintained and continues to maintain that levels of IGF-I in milk whether or not from rbGH supplemented cows are not significant when evaluated against the levels of IGF-I endogenously produced and present in humans.

We agree that IGF-I, like most proteins, would begin digestion in the stomach where pepsins would cleave some of the peptide linkages thereby generating polypeptides. However, digestion of proteins is more intensive in the small intestine and protein absorption occurs predominantly in the small intestine. While there is some indication that casein or other factors in milk may decrease initial protein digestion in the stomach, this does not establish that digestion does not

occur in the small intestine, where most protein digestion routinely occurs, or how much, if any, IGF-I is absorbed intact.

IGF-I is normally found in human plasma at concentrations much higher than those found in bovine milk (Schaff-Blass et al., 1984). The levels in human plasma range from a low in neonates of 14 ng/mL to a high of 686 ng/mL in late pubertal females. The mean values of IGF-I concentrations in human blood plasma are between 42-308 ng/mL. The total daily production of IGF-I (endogenously) in an adult is 10,000,000 ng/day (Guler et al., 1989). Additionally, IGF-I is normally found in human breast milk in concentrations higher than those found in bovine milk. The IGF-I concentrations in human milk ranged between 13 and 40 ng/mL six to eight weeks postpartum (Corps et al., 1988). Milk samples from 5 commercial dairy herds not supplemented with rbGH had a mean IGF-I concentration of 2.54 ng/mL.

Reported percentage increases in IGF-I concentrations in milk of rbGH supplemented cows can be misleading because the levels of IGF-I in milk are so low prior to any increase. For example, a 1988 study (Torkelson et al., 1988) indicated that while IGF-I concentrations in milk of rbGH treated cows could be as much as two-fold higher (a 100% increase) than unsupplemented cows, the absolute increase was only 2-3 ng/mL.

IGF-I is a normal but highly variable constituent of bovine milk with the concentration depending on the animal's stage of lactation, nutritional status and age. While some studies indicate that levels of IGF-I may statistically increase in the milk of rbGH supplemented cows relative to unsupplemented cows, reported increases are still within the normal variations of IGF-I levels in milk. Therefore, while IGF-I levels in milk from rbGH supplemented cows have been considered to be elevated by some groups (WHO FAS 41, 1998), IGF-I levels in milk from rbGH supplemented cows do not differ from those of unsupplemented cows in general.

The reported IGF-I absorption and increases in the circulating plasma levels of IGF-I reported in the literature (Heaney et al., 1999; Xian et al., 1995; Epstein 1996; and Kimura et al., 1997) must be viewed in light of the normal production of IGF-I in humans. The total daily adult endogenous production of IGF-I is in the milligram range while daily levels of IGF-I consumed in milk (by three-glass-a-day milk drinkers) are in the microgram range (a thousand-fold difference). As detailed below, IGF-I in milk would alter plasma levels by less than 1%--even if the entire amount of IGF-I in 1.5 liters (three very large glasses--an 8 oz. glass is less than a  $\frac{1}{4}$  liter) of milk were totally absorbed. Therefore, the percentage increases in serum IGF-I reported in some studies (e.g. Heaney et al., 1999) following milk consumption cannot possibly be due directly to IGF-I absorption from milk.

Finally, we note the study by Storm et al. (1998). This study utilized three treatment groups: placebo, non-dietary calcium, and milk supplementation. The milk group of 20 volunteer women consumed four 8-ounce glasses of milk every day for the 2-year duration of the trial. The women supplemented with milk had no significant change in serum IGF-I when compared to the women in the other groups.

The presence and the concentrations of IGF-I in bovine milk resulting from rbGH administration were addressed by the 1992 and 1998 meetings of JECFA. FDA scientists were invited to participate in these independent scientific meetings of international experts on food safety. Concerns about the biological significance of rbGH-induced increases of IGF-I levels in milk were thoroughly evaluated.

The 1992 JECFA expert committee reached the conclusion that any elevation of IGF-I levels in milk resulting from rbGH administration was not of any human health concern due to the lack of significant oral absorption of IGF-I under normal physiologic circumstances in humans. The 1998 JECFA expert committee concluded purely on the basis of exposure that the amount of IGF-I in milk is insignificant compared to the production of IGF-I in people (less than 0.09%). This amount, even if it all survived digestion (and there is insufficient credible evidence that it does), could not reasonably elevate human plasma levels by even 1%. The international experts, including those from the FDA, concluded that IGF-I levels in milk of rbGH supplemented cows do not produce a biologically significant or deleterious effect in people. This conclusion of safety is reinforced by the JECFA decision that an allowable daily intake (ADI) and maximum residual limits (MRL) in food are not needed for rbGH and that rbGH can be used without any appreciable risk to the health of consumers. We also note Health Canada's similar conclusion that "rbST-induced IGF-I (insulin growth factor) is insignificant when compared with naturally occurring IGF-I" (formal News Release summary).

### **3) The potential association between elevated IGF-I levels and cancer.**

Your petition also asserts that there is a connection between increases in levels of IGF-I and cancer. Specifically, your petition claims that "IGF-I is thought to be an important growth factor in breast cancer, prostate cancer and colon cancer" (Ng et al., 1998; Wolk et al., 1998; Lamonerie et al., 1995). The authors postulate in these articles an association between significant increases in the plasma levels of IGF-I and tumor appearance based on epidemiological observations. None of the articles demonstrate a causal relationship between IGF-I and the appearance of tumors. Further, while some of the articles purport an association between IGF-I and/or IGF-II and cancer, they do not focus on establishing a link between IGF-I and cancer (Ng et al., 1998; Lamonerie et al., 1995). Thus, while large percentage increases in IGF-I concentrations in human plasma are reported in association with some tumors, the authors of these articles do not reach the conclusion that IGF-I caused the tumors. These are not the first studies to link IGF-I and cancer. In fact, FDA's Report discussed similar studies and reached the same conclusion (i.e., that "IGF-I is not the causative agent" of cancer) that we reach here.

Among the growth factors, IGFs play a crucial role in regulating cell proliferation and differentiation. IGFs' mitogenic activity (activity on reproduction of the cell) is regulated by receptor binding, which is in turn facilitated by IGF-binding proteins. These articles note a possible dose-response relationship between increased risks of these cancers and elevated levels of IGF-I, but none of the three articles empirically demonstrates this type of relationship. The authors state that increased IGF-I plasma levels may be part of the phenotype of certain types of cancer; thus, the cancerous cells themselves may promote IGF-I to maintain their accelerated cell

cycle. That is, the increased IGF-I levels may be the result of the cancer, and characteristic of the cancer process, but not the cause.

While clearly debatable, if increased circulating IGF-I levels were assumed to increase cancer risk, then the interaction between IGF-I and its receptor and the binding proteins becomes important. The putative carcinogenic effects of IGF-I would then depend upon receptor interaction. IGF-I is not directly genotoxic (i.e., it does not directly alter the DNA). The ligand-receptor complex is responsible for the increased DNA synthesis and the acceleration of the cell cycle seen in the presence of IGF-I. There is no experimental evidence (1) that oral rbGH impacts the level of circulating IGF-I, or the number of IGF receptors and (2) that rbGH increases the number of ligand-receptor complexes. Thus, at present there is no evidence linking rbGH to any increased cancer risks that might be due to increased IGF-I and IGF receptor interactions. We reiterate that with respect to potential effects in humans, the amount of IGF-I in milk from cows (regardless of possible rbGH supplementation) is insignificant compared to the endogenous production of IGF-I in people (less than 0.09%).

#### **4) A possible relationship between rbGH and BSE.**

Another area of concern you addressed in your petition is a potential relationship between rbGH use and an increased risk of bovine spongiform encephalopathy (BSE) in dairy cows. To support your claim you reference Attachment 3, an unpublished paper by Hansen, et al. (1997). Quoting from your petition:

“There are two mechanism[s] whereby rbGH could potentially lead to an increase in BSE. First, increased circulating IGF-I levels might increase a cow’s susceptibility to BSE should an animal be exposed to the infectious agent. ... Second, rbGH treated cow’s increased protein feed needs could magnify the odds of exposure to a BSE-infective agent.”

BSE belongs to a group of progressive neurodegenerative diseases of humans and animals called the transmissible spongiform encephalopathies (TSEs), which include scrapie in sheep and Creutzfeldt-Jakob Disease in humans (Weber et al., 1997). The nature of this infective agent, called a "prion," is still imperfectly understood (Somerville et al., 1997; Hedge et al., 1999). A widely held theory is that the infectious agent is a protein; in fact, the term prion stands for “proteinaceous infectious” particles.

TSE infectivity has been associated with a protease resistant protein (PrP-res), which is a post-translationally modified form of the proteinase K-sensitive host-encoded prion protein (PrP-sen). The protein, PrP-sen, is normally found in all animals, however, the normal role played by PrP-sen protein in the nervous and lymph systems is unknown. Current theory holds that the abnormal form, PrP-res, causes the normal PrP-sen to convert to the abnormal PrP-res form in a cascade effect. PrP isoforms are routinely endocytosed through the cell membrane into the cell. However, the cell cannot digest the PrP-res molecules and, thus, the level of this resistant protein builds up in the cell, eventually causing cell death (Plum, 1997; Weber et al., 1997).

Your petition suggests, and the Hansen et al. paper more directly argues, that rbGH use might increase BSE risks through effects of IGF-I on prion gene expression. You note that Lasmezas et al. (1993) demonstrated that IGF-I significantly increased PrP-sen precursors in cell culture experiments. Given the cellular growth-promoting activity of IGF-I, it is not surprising that there is an increased transcription of genetic material with increased IGF-I. However, this *in vitro* study does not demonstrate a link between IGF-I and the encephalopathic PrP-res product. Nor does this article demonstrate that IGF-I is in any way associated with the conversion of the normal PrP-sen to the infective PrP-res product. To reiterate, the article only links IGF-I to the increased PrP-sen precursors, not to the generation of the modified PrP-res proteins.

You also note that an *in vivo* experiment with transgenic mice showed that the rate of scrapie progression increased after these mice were fed scrapie-infected hamster brains; this rate increase is relative to the mice not fed PrP-res (Prusiner, 1991). Given the model of TSE disease progression wherein PrP-res proteins are the etiologic agents of the neuropathies, it is not surprising that once these mice were fed prion-containing food the clinical manifestations of increased PrP-res levels resulted in more rapid scrapie development in the target animal (Kuczius and Groschup, 1999). The link between the PrP-sen precursor and TSE is speculative at best and the connection between this study and rbGH is not clear.

In order for rbGH to contribute to a BSE outbreak, the rbGH administered to the cows would have to elicit an increase in the IGF-I levels in the brains of the animals (by crossing the blood-brain barrier) to generate increased PrP gene expression. But even if PrP gene expression were enhanced there would be no link to BSE. Rather, the animal would need to be exposed to the PrP-res protein and subsequently experience the conversion of the PrP isoform to generate the pathology. More importantly, there is no evidence of BSE in the United States and thus, domestic cows have not been exposed to the agent.

We believe there is no possibility that an increase in IGF-I levels in milk could significantly impact the progression of human TSE for the same reasons that IGF-I in milk could have no significant impact on cancer.

Your petition also tries to establish a connection between increased feed consumption by rbGH-treated dairy cows and the risk of BSE. The FDA did, in fact, conclude that feed intake increases in cows supplemented with Posilac. This effect is consistent with the increased milk production of supplemented animals. Thus, consumption of all nutrients, including protein, would increase in animals treated with Posilac. However, in 1997 the FDA banned the use in ruminant feed of mammalian proteins that may be vectors for BSE. Feed manufacturers now rely on plant and other exempt sources of protein for dairy cattle feeds (21 CFR 589.2000; 62 FR 30976). This prohibition is a proactive measure by the U.S. government that would limit cattle exposure to the BSE agent should it ever occur in this country. Further, due to the recent history of BSE outbreaks in England, there is a worldwide ban on the export of all rendered ruminant material from the United Kingdom (Kimberlin, 1993; CEC, 1989; CEC, 1990; HMSO, 1990). These

prohibitions serve to limit the potential exposure of U.S. livestock to the resistant PrP, thereby, decreasing the risk of BSE pathology (Kimberlin, 1993; 62 FR 30976).

In conclusion, we note that the Hansen paper itself calls any link between BSE and rbGH "speculative" and states that "these conclusions are highly tentative because of the sparse nature of the evidence." The FDA agrees that the purported relationship between rbGH and BSE, a disease that does not even exist in the U.S. (62 FR 30976), is highly speculative.

#### **5) The FDA evaluation of human health risks**

Your petition states that "the Health Canada report reveals that to date the FDA has failed to fully evaluate the human health risk associated with oral exposure to rBGH." We disagree with this statement. First, we would like to note that the mandate of the Canadian internal review team (as presented and discussed in Attachments 1 and 2) was to conduct a "gaps analysis" on what needed to be done to support approval of rbGH by the Bureau of Veterinary Drugs' Human Safety Division. This evaluation included reviewing published literature and submissions from other drug companies on various formulations of rbGH. The review was not limited to Monsanto's rbGH product. The FDA's conclusions on the human food safety of Monsanto's rbGH are based on pivotal pre-approval studies conducted in accordance with good laboratory practices for which the Agency had access to individual animal data. Additionally, we note that the FDA previously dealt with many of the concerns within your petition (such as absorption of rbGH, elevation of IGF-I, and the relationship between IGF-I and cancer) in the FDA's Report, which was published February 10, 1999.

Once again, the final conclusion of the Canadian review was that, based on available evidence, they had no food safety concerns regarding rbGH. The Health Canada report "found no significant risk to human safety through ingestion of products from rbST-injected animals." Among its key findings were that "rbST poses no carcinogenic risk," and that "rbST-induced IGF-1 (insulin growth factor) is insignificant when compared with naturally-occurring IGF-1" (Health Canada's formal News Release summary from January 14, 1999).

In addition, as noted in previous sections of this response, an international panel of experts at the JECFA proceedings has evaluated the food safety of rbGH. JECFA's food safety reviews, in both 1992 and 1998, support the FDA conclusion regarding the safety of rbGH. Many other review bodies external to the FDA have also affirmed the agency's conclusion that Posilac is safe, including: the National Institutes of Health; the Congressional Office of Technology Assessment; the American Medical Association; and the American Dietetic Association.

## **II. Target Animal Health**

The FDA disagrees with the review approach taken by the Health Canada commissioned CVMA Expert Panel for determining the animal safety and effectiveness of the specific rbGH product,

Posilac. The following is excerpted from the Executive Summary of the report (provided as Attachment 1 to the amendment to your citizen petition):

“The Panel reviewed material provided by Health Canada from Monsanto’s submission to have rBST (sometribove) approved for use in Canada and carried out an extensive review of the published literature on the subject. While studies based on Monsanto’s product and other companies’ products were all considered, emphasis was placed on the former.” Page 1, 2<sup>nd</sup> paragraph.

The FDA’s conclusions on the animal safety and effectiveness of the Monsanto Posilac formulation of rbGH are based only on pre-approval studies and post-approval information for Posilac. Posilac is a sustained-release formulation of rbGH approved for subcutaneous injection of 500 mg rbGH every 14 days, starting during the 9<sup>th</sup> or 10<sup>th</sup> week after each calving and continuing until the end of each lactation. Results from studies of other rbGH formulations are not appropriate for evaluating Posilac because they may involve different formulations of rbGH, different dosing patterns (e.g., daily injectable vs. sustained-release), and different doses. Also, some studies reported in the scientific literature and included in the CVMA Expert Panel review used other rbGH products where treatment was initiated at different stages of lactation. Some began treatment as early as the 4<sup>th</sup> week of lactation, when dairy cows are typically at their most negative energy balance. Thus, animal safety and effectiveness of Posilac when used per approved labeling may be different from that observed for other rbGH products.

Even some of the studies using Posilac that were included in the review by the CVMA Expert Panel would be inappropriate for the pivotal determination of animal safety and effectiveness of the product as it is intended for use in the U.S. “Pivotal” studies are well-controlled studies specifically designed to evaluate safety and effectiveness under the intended conditions of use of the product. Examples of non-pivotal studies included in the CVMA Expert Panel review were research studies in which cows were treated for partial lactations. Also, studies of Posilac conducted in Europe would not be relevant for determination of the animal safety and effectiveness in the U.S. because of differences in management of dairy farms, animal genetics, nutrition, environment, etc. As noted, the FDA does require drug sponsors to submit all information on their drug prior to approval of the product, including results of non-pivotal studies. The FDA reviews this information to ensure that no adverse animal health or effectiveness problems are missed. However, the final determination of the animal safety and effectiveness of a new animal drug is primarily based on results of pivotal studies.

Additionally, we note that the CVMA Expert Panel relied extensively on reports in the scientific literature. These reports do not provide individual animal data, only the summarized results. The FDA reviews data from individual animals in pivotal studies to ensure that animals were appropriately managed in a controlled manner and that data were properly summarized and analyzed. It is not possible to perform such quality assurance steps with reports from the scientific literature.

## 6) Incidence of mastitis

Within your amendment to the citizen petition you expressed concern about the increased rates of mastitis associated with rbGH use. The following is excerpted from the Executive Summary of the CVMA Expert Panel report:

“Use of rBST increased the risk of clinical mastitis by approximately 25%. It appeared that there was also a slight increase in the prevalence of subclinical intramammary infections at the end of the treatment period. The Panel felt that while current dairy health management techniques could reduce this increased risk, they are not adequate to eliminate it.” Page 2, 2<sup>nd</sup> full paragraph.

The FDA approval of “production drugs,” that is, drugs that enhance the productivity of food-producing animals, does not mean that there are no risks of adverse effects to the treated animal. All animal health effects that are statistically increased by treatment with the drug are evaluated with respect to the degree of increase, the biological importance of the effect, and whether such a risk might be manageable under U.S. conditions (even if not necessarily eliminated). If the specific adverse effect is not of severe biological consequence and the level of increased risk is believed to be manageable, the drug may be approved and the risks described on the product label. Producers then can decide whether use of the drug would be appropriate under their conditions of operation. Producers can also discontinue use of the product if they find that it is not economical or beneficial to their business. The FDA noted that animal health risks associated with the use of rbGH were problems already observed on U.S. dairy farms and that approved management methods existed for reducing these risks.

As reported on the labeling for Posilac and in the FOI Summary (Section 6.j.), the FDA concluded that cows injected with Posilac are at an increased risk for clinical mastitis. The number of cows affected and number of cases per cow may increase. In addition, the risk of subclinical mastitis is increased. Also, in some herds, milk somatic cell count might increase. The label indicates that the use of Posilac is associated with increased frequency of mastitis treatment. The label concludes, “Mastitis management practices should be thoroughly evaluated prior to initiating use of Posilac.” The 28-herd (1213 cow) study associated with Monsanto’s Post-Approval Monitoring Program (PAMP) and post-approval adverse drug experience (ADE) reporting confirms that use of Posilac is associated with a statistically significant increase in clinical mastitis. Thus, your petition as amended has introduced no new information regarding mastitis incidence in dairy cows treated with Posilac.

The FDA determined that supplementation with rbGH caused approximately 0.15 extra cases of mastitis per cow per 305-day lactation. In making the decision to approve Posilac, the FDA concluded that the variation in mastitis incidence (due to season, parity, stage of lactation, and herd-to-herd variation) that occurred in U.S. cows not treated with Posilac was considerably

greater than the effects of Posilac treatment. It was also noted that mastitis cases in Posilac-treated cows were not more difficult to treat than cases in control cows and were of similar duration. Thus, FDA concluded that the increased risk of mastitis due to Posilac treatment would be manageable under normal U.S. conditions. FDA's conclusion was supported by the fact that the incidence of mastitis reported in the 28-herd PAMP fell below the predicted 0.15 extra cases per cow treated with Posilac.

We also note that FDA's evaluation of the impact of Posilac on milk production was based on salable milk. This addresses and supports the effectiveness of the product: cows treated with Posilac produced significantly more milk than untreated cows even after discarding milk due to mastitis or therapy for mastitis.

Your citizen petition amendment mentions an August 1992 report by the General Accounting Office (GAO) on mastitis in cows treated with rbGH. That report was focused on a potential indirect human safety concern, questioning whether there might be increased antibiotic residues in food products from cows treated for mastitis. On March 31, 1993, the FDA brought these concerns to its Veterinary Medicine Advisory Committee and expert consultants for an open public hearing. The committee agreed with the FDA's conclusion that the effect of Posilac use on the incidence of mastitis was much less than other factors, and that adequate safeguards are in place to prevent unsafe residues of antibiotics used to treat mastitis from entering the milk supply.

#### **7) Incidence of lameness**

Another target animal safety concern you present in the amended petition is reported increased rates of lameness resulting from rbGH use:

“Treated cows experienced approximately a 50% increase in the risk of clinical lameness. Many of the lameness cases involved fore and hind limb joints. The Panel felt that current health management practices were not able to eliminate this increased risk.” Page 2, 4<sup>th</sup> full paragraph of the Executive Summary of the CVMA Report.

The FDA thoroughly evaluated the effect of Posilac treatment on the musculoskeletal system of cows prior to approval (see Section 6.f. of the FOI Summary). In addition to daily health observations of all cows in the pivotal pre-approval studies, one of the pre-approval studies provided an extensive evaluation of lameness and joint lesions in a 188 dairy cow field trial conducted on 8 commercial dairy herds. Two veterinary experts in the study of lameness in dairy cattle evaluated the locomotion and the physical condition of the limbs. Based on results from these studies, the FDA concluded that cows injected with Posilac had increased numbers of enlarged hocks (rear leg joint) and lesions (e.g., lacerations, enlargements, calluses) of the knee (front leg joint). Also, second lactation or older cows had more disorders of the foot region. These effects are described on product labeling. However, evaluation of the pivotal pre-approval

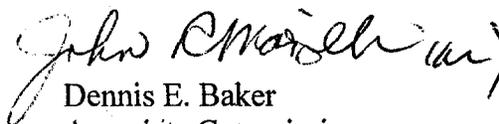
The FDA agrees that the incidence of retained placenta may be higher in cows treated with Posilac, and again this is indicated on product labeling (Section 6.k. of the FOI Summary). However, a thorough evaluation by the FDA of pre-approval data indicated that abortions/fetal losses were not increased in Posilac-treated cows (Section 6.i. of the FOI Summary). Also, results of the 28-herd PAMP study and post-approval ADE reports confirmed that abortions/fetal losses are not increased in treated cows.

To summarize, the amended petition provides no new information regarding the effects of Posilac treatment on reproductive performance in dairy cows.

### **Conclusion**

In conclusion, the approval of Posilac in the U.S. was based upon careful review of well-controlled studies providing adequate data to evaluate effects on human food safety and target animal safety. Extensive post-approval monitoring support FDA's initial conclusions regarding target animal safety. Extensive consideration of food safety issues by Health Canada and WHO/FAO's JECFA support FDA's conclusions regarding food safety. The FDA continues to conclude that those U.S. dairy producers choosing to use it can use Posilac safely and effectively. The petition provides no basis for withdrawing the approval of Posilac. For the reasons presented, we deny your Citizen Petition requesting withdrawal of the approval of the New Animal Drug Application providing for the marketing of Posilac by Monsanto. Also, as stated above, the FDA does not have the authority to suspend approval of Posilac under the imminent hazard provision in section 512 (e)(1) of the Act. That authority is vested in the Secretary, or in her absence, the officer acting as Secretary. Since the issues you raised do not support withdrawal of the new animal drug application for Posilac, we believe those issues also would not support a suspension of the application based on imminent hazard by the Secretary.

Sincerely yours,



Dennis E. Baker  
Associate Commissioner  
for Regulatory Affairs

cc: HFA-305 (Docket 98P-1194)

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