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Re: Docket No. FDA-2007-P-0119 (previously 2007P-0059/CP1)

Dear Dr. Epstein, Mr. Cummins, Dr. Peck, Dr. P Pusztai, and Mr. Smith:

This is the final response to your Citizen Petition dated February 20, 2007 (CP #2007P-0059/CP1, updated to CP #FDA-2007-P-0119) concerning Posilac^{®1} (somatotrophic zinc suspension), a recombinant bovine growth hormone (rbGH) product (also known as rBGH, recombinant bovine somatotropin, and rbST). On January 26, 2010, you submitted an amended petition, dated May 11, 2007.

Posilac was originally sponsored by the Monsanto Corporation (Monsanto) and approved for marketing by the Food and Drug Administration (FDA) on November 5, 1993. Posilac is now sponsored by Elanco Animal Health (Elanco), a Division of Eli Lilly & Company.

¹ Posilac[®] is a registered trademark for Elanco's rbGH product with the United States Patent and Trademark Office.

You requested that:

The Secretary of Health and Human Services (HHS) and the Commissioner of Food and Drugs "[s]uspend approval of Posilac, and/or require milk and other dairy products produced with the use of Posilac to be labeled with warnings such as, 'Produced with the use of Posilac, and contains elevated levels of IGF-1, a major risk factor for breast, prostate, and colon cancers.'"

You state that your petition is based on scientific evidence of increased risk of cancer, particularly breast, colon, and prostate, from the consumption of milk from cows injected with Posilac, and abnormalities in the composition of milk from rbGH-treated cows, resulting from the "recognized veterinary toxicity of rbGH, particularly increased levels of IGF-1."

Your petition raises nine main areas of concern. The specific issues that you raise with regard to Posilac are that:

- 1) Posilac is toxic to treated cows and results in contamination of milk with medications and antibiotics;
- 2) Milk of treated cows is abnormal in composition;
- 3) There are increased levels of IGF-1 in milk from treated cows;
- 4) IGF-1 is absorbed from the intestine into the blood;
- 5) Increased IGF-1 levels increase risks of breast, colon, and prostate cancers
- 6) Increased IGF-1 levels inhibit apoptosis;
- 7) rbGH increases twinning rates;
- 8) Use of rbGH and dairy products from treated cows is banned in other countries; and
- 9) FDA's labeling policy for milk from rbGH-treated cows is inadequate.

FDA has thoroughly reviewed the issues raised in your petition. For the reasons discussed below, your petition is denied.

BACKGROUND:

Prior to commercial distribution of any new animal drug for use in food-producing animals, a sponsor must provide evidence to establish that its product is safe and effective for its intended uses. Section 512 of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 360b; 21 CFR 514.1(b)(8). The safety determination for new animal drugs takes into account a number of factors including the likelihood that the drug or a substance formed in food because of the drug will be consumed by humans, the cumulative effects of the drug on the animal or humans consuming food products derived from that animal, safety factors that experts consider appropriate for extrapolating from animal experimentation data, and whether the conditions of use suggested in the labeling are likely to be followed. Section 512(d)(2) of the Act, 21 U.S.C. 360b(d)(2).

In short, a new animal drug will not be approved unless it is deemed safe both for the target animal species and humans who consume food derived from treated animals. A new animal drug is deemed effective when, on the basis of substantial evidence, the sponsor demonstrates that the product consistently and uniformly has the effect the sponsor claims it is supposed to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling of the drug. Furthermore, the sponsor must prove that it can consistently manufacture the drug to a specific purity, potency, and quality. Section 512(d)(1)(C) of the Act, 21 U.S.C. 360b(d)(1)(C); 21 CFR 211 et seq.

Milk and other dairy products are labeled according to the Act's provisions governing food misbranding. Under section 403(a)(1) of the Act, a food is misbranded if its labeling is false or misleading in any particular. Section 201(n) further requires that the label of a food must reveal all material facts about the food. Under 201(n), labeling is misleading, and therefore the product is misbranded under section 403(a)(1), if it fails to reveal facts that are material in light of representations made or suggested in the labeling, with respect to consequences which may result from the use of the article to which the labeling relates, or under such conditions of use as are customary or usual.

After reviewing the data submitted in support of the new animal drug application for Posilac, FDA concluded that Posilac administered by subcutaneous injection as 500 mg of rbGH every 14 days, starting during the 9th to 10th week of lactation, is safe and effective for its intended use in healthy lactating dairy cows. In addition, the Agency found that there was no significant difference between milk from cows treated with rbGH and milk from cows that have not been treated with rbGH. Accordingly, the Agency concluded that the fact that milk was produced by a cow that had been administered rbGH is not material information within the meaning of section 201(n) of the Act, and, as such, did not require any additional labeling on such articles. Additional details related to FDA's conclusions regarding Posilac can be found in the FDA's Freedom of Information (FOI) Summary for Posilac (NADA 140-872) (FOI Summary), available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm050022.pdf>. Additional details related to FDA's labeling determination concerning milk produced by cows that have been administered rbGH can be found in the "Interim Guidance on the Voluntary Labeling of Milk and Milk Products From Cows That Have Not Been Treated With Recombinant Bovine Somatotropin" (Interim Guidance), 59 Fed. Reg. 6279 (1994).

In your Petition, you ask that FDA suspend approval of the new animal drug application for Posilac based on the imminent hazard authority granted under section 512(e)(1) of the Act, which provides that the FDA may suspend the application of a new animal drug where the Secretary "finds that there is an imminent hazard to the health of man or of the animals for which such drug is intended." This authority is not delegated to the Commissioner of Foods and Drugs. Nevertheless, we have evaluated your request to determine whether FDA should recommend such action to the Secretary. As detailed in the following paragraphs, FDA believes that the arguments presented in your petition do not demonstrate a basis for suspending approval of the new animal drug application for

Posilac. Furthermore, your petition does not provide a basis for initiating proceedings to withdraw the approval of Posilac.

You also request that FDA "label milk and other dairy products produced with the use of Posilac with a cancer risk warning" and further state that FDA's current policy on labeling milk produced by cows that have been administered rbGH is misleading. FDA believes that the arguments presented in your petition do not demonstrate any basis for requiring your proposed warnings or changing FDA's current labeling requirements.

FDA's responses to the nine concerns described in the "Statement of Grounds" section of your petition are provided below:

1. The Veterinary Toxicity of Posilac.

You assert that Monsanto and FDA initially suppressed information about "toxic effects" of rbGH in "secret" nationwide trials prior to October 1989, after which details were disclosed on the drug's labeling in November 1993. You state that these veterinary toxic effects include injection site lesions, a wide range of other toxic effects, and an increased incidence of mastitis, requiring the use of medication and antibiotics, and resulting in contamination of milk.

FDA thoroughly evaluated the safety of Posilac in its pre-approval review of the drug application. See FOI Summary. In addition, in 1994, these issues were brought before a federal district court judge in Wisconsin, who found that FDA was not arbitrary or capricious in approving the drug. See Stauber v. Shalala, 895 F.Supp. 1178 (W.D. Wis., 1995). We refer you to these documents for a more thorough discussion of these issues.

In addition, with respect to your concern that an increased incidence of mastitis requires the use of medication and antibiotics, and results in contamination of milk, FDA notes that Monsanto conducted an extensive post-approval monitoring program to ensure that Posilac's use in cows did not lead to an increased incidence of violative antibiotic residues in the milk supply in the United States.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) similarly concluded in 1998 that the use of rbGH would not result in a higher risk to human health due to the use of antibiotics to treat mastitis. Evaluation of Certain Veterinary Drug Residues in Food, Fiftieth report of the Joint FAO/WHO Expert Committee on Food Additives, 74-76 (1999) (JECFA Fiftieth report), http://whqlibdoc.who.int/trs/WHO_TRS_888.pdf [hereinafter JECFA Fiftieth report]. This decision was reaffirmed at the seventy-eighth meeting of the organization held November 5-14, 2013. See Joint FAO/WHO Expert Committee on Food Additives, Seventy-Eighth Meeting Summary Report (Seventy-Eighth Meeting), at 5, http://www.fao.org/fileadmin/templates/agns/pdf/jecfa/JECFA_78_Summary_report_Version_final.pdf [hereinafter Seventy-Eighth Meeting].

Your assertion that FDA and the sponsor inappropriately hid data is baseless. Pursuant to Federal law, FDA is obligated to maintain the confidentiality of data and information in new animal drug applications and investigational new animal drug notices as described in Part 21 of the CFR Chapter 514.11 and 514.12, respectively. After the approval of the new animal drug, an FOI Summary is made available to the public which summarizes the safety and effectiveness data on which the approval was based (21 CFR 514.11(e)). FDA appropriately maintained the confidentiality of information on the studies conducted and the effects of Posilac on animal safety until the drug was approved on November 5, 1993, at which time we released a summary of safety and effectiveness information on the safety and efficacy of Posilac, pursuant to 21 CFR 514.11.

Further, FDA's review of rbGH was scrutinized by both the HHS Office of Inspector General (OIG) and by the Government Accountability Office (GAO). In a memorandum dated February 21, 1992, the OIG announced that it had found no evidence that indicated that FDA or Monsanto engaged in manipulation or suppression of animal health test data. See <http://oig.hhs.gov/oas/reports/phs/c9000046.pdf>. Likewise, an August 6, 1992, GAO report concluded that FDA's review of rbGH had met all established guidelines. GAO/PEMD-92-26, "Recombinant Bovine Growth Hormone -- FDA Approval Should Be Withheld Until the Mastitis Issue is Resolved," <http://archive.gao.gov/d33t10/147302.pdf>.

2. Abnormalities in rbGH Milk

You state that there is a wide range of well-documented abnormalities in milk from rbGH-treated cows, apart from increased IGF-1 levels, including:

- a. Reduction in casein, reduction in short-chain fatty acid and increase in long-chain fatty acid levels;
- b. Increase in levels of the thyroid hormone triiodothyronine enzyme;
- c. Contamination with unapproved drugs for treating mastitis; and
- d. Frequency of pus cells due to mastitis.

When FDA approved Posilac in 1993, it concluded that there was no significant effect of treatment on general milk composition, including milk fat, protein, lactose, calcium, and phosphorus percentage. See FOI Summary at 18-19. The following is FDA's response to each major concern raised in your petition related to milk from rbGH-treated cows.

- a. Reduction in casein, reduction in short-chain fatty acid and increase in long-chain fatty acid levels.

Your claim of reduced concentrations of casein and short-chain fatty acids (FA) and increased concentration of long-chain FA in milk of treated cows was based on your Reference #3, Baer RJ et al. In this study, cows were treated with 30.9

mg rbGH a day for 13 weeks (weeks 15 through 28 after calving). The formulation, dosage, and treatment duration were not consistent with the approved administration of Posilac, which is 500 mg rbGH given every 14 days in a prolonged-release formulation, starting weeks 9-10 (57-70 days) after calving and continuing until the end of the lactation period, which, on average, lasts about 305 days (43 weeks). Therefore, the allegations you make are not substantiated with respect to the approved use of Posilac. Even with the study using a different formulation, dosage, and duration of administration than the approved product, out of 15 variables measured in the Baer study (14 in milk and 1 in serum), only 4 were significantly different between rbGH-treated and control cows. These were serum protein (increased from 0.65 to 0.71%), lactose in milk (increased from 4.71 to 4.80%), casein in milk as a percentage of total protein (decreased from 75.5 to 73.9%), and casein in milk as a percentage of true protein (decreased from 80.2 to 78.8%). Contrary to your assertion, the percentage of total casein in milk was not statistically significantly different between the two treatment groups. The changes in milk concentrations of short- and long-chain FA in the Baer study, although statistically significant, were biologically insignificant because they were within the normal variation of these components in cows' milk. Factors such as stage of lactation, nutrition, and breed of dairy cows have a much greater effect on these components of milk.²

A long-term study by Barbano et al., reported in two publications and not cited in your petition, provided more accurate information on the effects of Posilac on milk composition than the study by Baer et al. because cows in the Barbano study were treated with the same formulation, dosage, and duration of treatment as approved for Posilac, i.e., 500 mg rbGH in a prolonged-release formulation every 14 days beginning at approximately 60 days after calving until the end of lactation or 25 injections (approximately 410 days after calving). Barbano, D.M., J.M. Lynch, D.E. Bauman, G.F. Hartnell, R.L. Hintz, and M.A. Nemeth, "Effect of a prolonged-release formulation of N-methionyl bovine somatotropin (sometribove) on milk composition," 75 J. DAIRY SCI. 1775 (1992); Lynch, J.M., D.M. Barbano, and D.E. Bauman, "Effect of a prolonged-release formulation of N-methionyl bovine somatotropin (sometribove) on milk fat," 75 J. DAIRY SCI. 1794 (1992). FDA reviewed these two publications during its review of the new animal drug application for Posilac. Compared to controls, concentration of milk casein in rbGH-treated cows was not different over the treatment period. Relative percentages of specific caseins also were not affected in rbGH-treated cows. Total fat percentage and fatty acid composition of milk fat were not affected by rbGH treatment of cows.

- b. Increase in levels of the thyroid hormone triiodothyronine enzyme.

² J.G. Linn, Factors Affecting the Composition of Milk from Dairy Cows. Designing Foods: Animal Product Options in the Marketplace. National Research Council (US) Committee on Technological Options to Improve the Nutritional Attributes of Animal Products. Washington (DC): National Academies Press (US); 1988.

With regard to “thyroid hormone triiodothyronine enzyme,” we assume you mean the enzyme thyroxine-5'-monodeiodinase, which catalyzes (facilitates) conversion of thyroid hormone thyroxine (T_4) to the more biologically potent thyroid hormone triiodothyronine (T_3). The 1989 paper by Capuco et al. that you cited [Reference #4] does not support your assertion that milk from rbGH-treated cows has increased levels of this enzyme. FDA reviewed this study during its evaluation of the new animal drug application for Posilac. In this paper, the authors reported increased thyroxine-5'-monodeiodinase activity in lactating mammary tissue of cows treated with 40 mg rbGH per day for 5 days. Again, this study used a different formulation of somatotribove zinc and used that different formulation at a substantially different dose and duration of treatment compared to the approved use of Posilac. They concluded that this result supported their hypothesis that rbGH treatment increases milk production via an increase in thyroxine-5'-monodeiodinase activity in mammary tissues. However, they did not measure nor discuss any changes in milk composition of rbGH-treated cows. The authors detected increased T_3 levels in mammary tissue of rbGH-treated cows versus controls, but no differences in T_3 or T_4 levels were found in serum, kidney, or liver tissues. The ratios of serum T_3/T_4 levels were also unaffected in these tissues. Thus, the Capuco et al. paper does not support your assertion that levels of thyroxine-5'-monodeiodinase in milk are increased in rbGH-treated cows.

c. Contamination with unapproved drugs for treating mastitis.

Your references supporting this assertion were all dated before FDA approved Posilac in 1993, and were taken into consideration in FDA's decision to approve Posilac.

This issue was fully litigated in Stauber and the court found that FDA considered the relevant factors and that FDA's determination that the current milk regulatory system would continue to ensure the safety of milk was not arbitrary. Stauber v. Shalala, 895 F.Supp. 1178, 1192 (W.D. Wis., 1995). The post-approval monitoring program for Posilac further supported FDA's conclusion that use of Posilac in dairy cows would not lead to an increased incidence of violative antibiotic residues in the milk supply in the United States. JECFA Fiftieth report. We refer you to these documents for a more thorough discussion of the issue.

d. Frequency of pus cells due to mastitis.

We assume that by “pus cells” you are referring to somatic cell count (SCC) in milk, because SCC increases as a result of an increased number of leukocytes, which are also found in pus. We use the term SCC because it is an established term in the scientific literature and veterinary practice and because the method for determining SCC does not distinguish between various cell types found in milk but counts all cell types together. Somatic cells are always present in milk and consist of heterogeneous populations of cells, including lymphocytes, neutrophils, macrophages, and epithelial cells. Somatic cell count is an indicator of the level

of inflammatory response of the udder and an increase is associated with an increase in mastitis. On its own, SCC is also typically considered to be more of an indication of the quality of the milk and its suitability for a given purpose (for example, cheese manufacture), rather than its safety for human consumption.

The 1992 discussion paper by Mepham [Reference #8] contained no original experimental data. The paper discussed mastitis, but not SCC. It cited an increased incidence of mastitis in rbGH-treated cows, based on a paper by Cole et al. Cole et. al., "Response of dairy cows to high doses of a sustained-release bovine somatotropin administered during two lactations. 2. Health and reproduction," 75 J. DAIRY SCI. 111 (1992). The Cole study used the Posilac formulation at doses 1.2, 3.6, and 6.0 times the approved dose and was considered in the evaluation of the effect of Posilac on safety to treated cows (See FOI Summary at 26-35; Multi-lactation Chronic Animal Toxicity Study (TAS), Study No. 100-DDC-COW-PJE-85-010).

The effects of rbGH on SCC in milk are discussed by Millstone et al. [Reference #9], but this 1994 article was a commentary, with no original experimental data. This paper discussed using different methods to analyze data on the effects of rbGH. Although the paper disagreed with the statistical methods used by Monsanto and accepted by FDA, it arrived at the same conclusion as FDA, namely that dairy cows treated with rbGH may have higher milk SCC.

As noted previously, when FDA approved Posilac in 1993, it concluded that treated cows may have higher milk SCC. Also as indicated previously, product labeling informs users of this potential. In the U.S., the legal maximum bulk tank level of SCC for Grade A milk shipments (i.e., milk that qualifies for fluid consumption) is 750,000 cells/mL, in accordance with the 2009 "Grade 'A' Pasteurized Milk Ordinance" issued by FDA, <http://www.fda.gov/downloads/Food/FoodSafety/Product-SpecificInformation/MilkSafety/NationalConferenceonInterstateMilkShipmentsNCIMSModelDocuments/UCM209789.pdf>. If a producer has two out of four shipments that test above the maximum 750,000 cell/mL limit (usually tested 30 to 45 days apart), a written notice is issued and an additional sample is tested within 21 days. If three of the last five counts exceed the maximum limit, immediate suspension of the producers permit and/or court action is instituted. Id. at 24. In other words, there are measures in place to prevent milk entering the food supply with an elevated SCC, regardless of its source, rendering this concern moot.

3. Increased Levels of IGF-1 in rbGH Milk.

You state that a wide range of publications have documented excess levels of IGF-1 in rbGH milk, and you include several publications [References #10-22] to support that claim. The references include peer-reviewed scientific articles with [References #11; 14; 15] or without [Reference #13; 16; 20; 22] new experimental data, as well as

non-peer-reviewed articles, such as conference abstracts [References #12; 21], statements/reports [References #10; 17; 18], and a magazine article [Reference #19]. All of the references except the 1994 Epstein article [Reference #19] and 1994 Mephram paper [Reference #20] were published prior to FDA's 1993 approval of Posilac. However, the Epstein and Mephram papers provided no original data. As such, the information contained in these references was evaluated and taken into consideration in FDA's decision to approve Posilac in 1993. In fact, several issues mentioned in your 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" (FDA report), available at <http://www.fda.gov/animalveterinary/safetyhealth/productsafetyinformation/ucm130321.htm>. Thus, the references provide FDA no new evidence to support the claim in your petition.

Following are FDA's responses to your predominant concerns:

- a. Milk IGF-1 levels increased 4- to 20-fold or more than 10-fold.

Your petition claims that milk IGF-1 levels increase 4- to 20-fold or more than 10-fold. Your petition cited articles with original experimental data [References #11; 14; 15] in support of elevated IGF-1 secretion in milk of rbGH-treated cows. We have thoroughly reviewed the references and have found that they do not support this conclusion. For example, the publication by Davis et al. [Reference #11] did not report measuring IGF-1 levels in milk, but only in serum; and the article by Francis et al. [Reference #14] reported a detection of IGF-1 and II in bovine colostrum by high performance liquid chromatography in animals that did not receive rbGH treatment.

The article by Prosser et al. [Reference #15] reported levels of IGF-1 in milk of rbGH-treated cows (30 mg/day s/c daily for 7 consecutive days). The design of this study did not include control animals, but rather reported average daily concentrations of IGF-1 in milk between 7 days before and 21 days after the initiation of rbGH treatment that lasted for 7 consecutive days. The peak IGF-1 concentrations in milk were recorded 7 days after the initiation of rbGH treatment (1.60 nmol/L), while the baseline levels were 0.44 nmol/L. It again should be noted that the study did not represent the approved dosage regimen for Posilac, in which 500 mg of rbGH is administered s/c every 14 days, starting during the 9th to 10th week of lactation in dairy cows. Nevertheless, the 4-fold increase in milk IGF-1 levels was well within the normal variation seen in non-treated dairy cows and not a human food safety concern. For example, as reported in the original FOI Summary, a survey study of 5 dairy farms in Missouri where cows were never treated with rbGH found that milk IGF-1 levels in individual cows varied from 0 to 30 ng/mL (which is equivalent to 0 to 3.92 nmol/L); farm variation was 0.29-4.21 ng/mL (i.e., 0.038-0.55 nmol/L). FOI Summary at 128-129.

Additionally, your petition cited a letter in Lancet by Mepham [Reference #20] but, as previously mentioned, it does not provide any original experimental data. The 1990 review article by Juskevich and Guyer [Reference #16] also supports an increased IGF-1 level in milk of rbGH-treated cows, but only about 2-fold, rather than 10-fold. Again, a 2-fold increase in IGF-1 is well within the normal range of levels found in milk of untreated cows and not a human food safety concern. None of the referenced articles demonstrate that the milk IGF-1 levels in rbGH supplemented animals are increased 10-fold or more, as claimed in your petition.

- b. IGF-1 level in milk increases by pasteurization by 70%.

Your petition claims that the levels of IGF-1 in milk increase by pasteurization by 70%. To support this claim, you cite articles by Juskevich and Guyer [Reference #16] and reports by JECFA [Reference #18] and the National Institutes of Health (NIH) [Reference #17]. Juskevich and Guyer [Reference #16] reported that pasteurization does not reduce IGF-1 levels in milk. The mean IGF-1 concentrations in raw milk and pasteurized milk samples were 5.6 ± 0.56 and 8.2 ± 0.35 ng/mL, respectively. However, as reported by Juskevich and Guyer [Reference #16], when milk was subjected to conditions similar to those in the procedure for making infant formula, IGF-1 levels were reduced to levels at or below approximately 0.5 mg/mL, well below normal physiological levels for cows' milk. The JECFA report [Reference #18] also does not support the claim that pasteurization increases IGF-1 concentration in milk. Instead, it concludes that IGF-1 is not destroyed by pasteurization, but that "the heating of milk for the production of infant formula reduces the amount of IGF-1 by at least 50%", and that "[h]uman breast milk contains IGF-1 concentrations similar to those found in milk from control and rbGH-treated cows." The conclusions of the NIH report [Reference #17] are very similar to the JECFA report.

To summarize, the cited literature supports the conclusion that pasteurization does not reduce IGF-1 in milk, but not the claim that pasteurization increases the concentration of IGF-1 in milk.

- c. Analytic techniques may underestimate IGF-1 levels by up to 40-fold.

Your petition claims that analytical techniques may underestimate IGF-1 levels in milk by up to 40-fold. In support of this claim, you submitted articles by Millstone et al., [Reference #9] and Prosser et al., [Reference #15]. The article by Millstone [Reference #9] does not report any new experimental results nor does it discuss IGF-1 levels in milk. Rather, it discusses a novel method for statistical analysis of the existing data. The article by Prosser et al. [Reference #15] tested a hypothesis that rbGH does not act on the mammary gland directly, but *via* IGF-1. The authors treated cows with 30 mg/dL rbGH s/c for 7 consecutive days. IGF-1 levels were measured in plasma and milk by radioimmunoassay. The limit of sensitivity of the test for IGF-1 was 0.07 nmol/L. The intra- and inter-assay variations were 9% and 19%, respectively. The paper reported that the average

IGF-1 levels in milk were increased in rbGH-treated cows as compared to control subjects. The majority (81%) of IGF-1 in milk was bound to proteins the sizes of which varied between 40 and 150 kDa. The remaining 19% of IGF-1 was present in milk in the unbound form. Furthermore, IGF-1 levels were correlated with milk yield in rbGH-treated cows. The authors stated that the milk IGF-1 levels in rbGH-treated cows are lower than those in early stages of lactation in non-treated cows. The authors further concluded that rbGH treatment raised the IGF-1 level in cow's milk only to concentrations equal to that of human milk collected in the sixth week of lactation. In conclusion, neither of the cited articles [References #9; 15] support your claim that the analytic techniques may underestimate IGF-1 levels by up to 40-fold.

4. IGF-1 is Readily Absorbed from the Intestine into the Blood.

It is well known that IGF-1 consists of 50 amino acids (National Library of Medicine protein accession number Q27962, <http://www.ncbi.nlm.nih.gov/protein/75059172>) and it can be considered either a small protein or a large polypeptide. Digestive processes can render biologically active peptides and proteins inactive when administered orally. The article by Juskevich and Guyer [Reference #16] discussed intestinal absorption of proteins and peptides, which may be absorbed in the intestines. However, these authors also noted that the amounts of absorbed proteins are on the order of 1:10,000 to 1:50,000 of the protein load given orally. Therefore, even the highest increase in IGF-1 in milk (e.g., 4X physiological values), were it to be absorbed at the highest rate of intestinal absorption of 1:10,000, would result in increased IGF-1 levels in human plasma of 1/2500 of physiological levels, which is negligible.

In addition, none of the articles cited in your petition provided evidence that IGF-1 is absorbed from the intestine into blood in the amounts that could affect milk consumers. The Juskevich and Guyer article [Reference #16] reported that recombinant IGF-1 orally administered to rats at doses of 0.01, 0.1 and 1.0 mg/kg body weight/day for two weeks did not result in any effects on body size, organ weights, pathology, or animal well-being. The other article cited [Reference #22] in support of the oral absorption claim does not present new experimental data supporting this claim.

The 1998 JECFA expert committee concluded, purely on the basis of exposure, that the amount of IGF-1 in milk is insignificant compared to the production of IGF-1 in people (less than 0.09%). This amount, even if all survived digestion (and there is insufficient evidence that it does), could not reasonably elevate human plasma levels by even 1%. Consequently, the international experts making up the JECFA committee, including those from FDA, concluded that IGF-1 levels in milk of rbGH-supplemented cows do not produce a biologically significant or deleterious effect in people. JECFA Fiftieth report at 77-78.

5. Increased IGF-1 Levels (in blood³) Increase Risks of Breast, Colon and Prostate Cancers.

You assert that there is a connection between increases in levels of IGF-1 and breast cancer [References #23-41], colon cancer [References #42-51], and prostate cancer [References #52-57].

None of your references demonstrate a causal relationship between dietary increase of IGF-1 levels and the appearance of tumors. In addition, none of the articles demonstrate a direct relationship between the IGF-1 levels in milk and those in consumers' blood circulation. Furthermore, while large percentage increases in IGF-1 concentrations in human plasma are reported in association with some tumors, the authors of these articles do not reach the conclusion that IGF-1 caused the tumors. These are not the first studies to associate IGF-1 and cancer and it is a well-established concept in the scientific literature that various components of the IGF system are involved in cancer development by either promoting or suppressing progression of some cancers. The FDA report discussed similar studies and reached the same conclusion (i.e., that "IGF-1 is not the causative agent" of cancer) that we reach here. See <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm130321.htm>.

6. Increased IGF-1 levels (in blood³) inhibit apoptosis.

You state that increased IGF-1 levels inhibit apoptosis, which may block natural defense mechanisms against the growth and development of early cancers [References #53, 58, and 59]. Apoptosis is the death of cells that occurs as a normal and controlled part of an organism's growth or development. Defects in apoptosis likely play a role in the pathogenesis of cancer and other diseases.⁴

The study by Chan et al. [Reference #53] did not measure the effect of IGF-1 in blood or other media on cell apoptosis, but rather, it prospectively evaluated levels of plasma IGF-1 and eventual prostate cancer occurrence in men. The study by Resnicoff et al. [Reference #58] found that the IGF-1 receptor protected tumor cells from apoptosis *in vivo*, and the authors noted that, when IGF-1 bound to its receptor, it likely activated the receptor. The study by Perks et al [Reference #59] examined the effect of various IGF-1 binding proteins, independent of IGF-1 itself, on apoptosis in breast epithelial cells *in vitro*.

As noted previously, it is well-established in the scientific literature that various components of the IGF system are involved in cancer development. However, none of your references demonstrate a relationship between dietary IGF-1 levels and levels of IGF-1 in consumers' blood circulation, much less the incidence of cancer. Also as

³ Reviewer's comment, based on the context.

⁴ Wong, RSY, "Apoptosis in cancer: from pathogenesis to treatment," 30 J. Exp. & Clin. Cancer Res. 87 (2011), <http://www.jeccr.com/content/pdf/1756-9966-30-87.pdf>.

discussed previously, IGF-1 levels in the milk of rbGH-treated dairy cows are well within the normal range of levels found in milk of untreated cows. Furthermore, intestinal absorption of IGF-1 is negligible.

7. rbGH increases twinning rates.

You stated that "An increased rate of twinning in cows injected with rbGH was admitted by Monsanto on its November 1993 Posilac label." When Posilac was originally approved in 1993, the FDA concluded that its use may increase multiple births in treated cows (See FOI Summary at 81-86), and a precaution stating this was required by FDA on product labeling. However, after evaluation of additional data from a 28-herd post-approval monitoring program study, the FDA concluded that Posilac use did not increase the rate of multiple births in treated cows, and the precaution was removed from Posilac labeling via a supplemental approval to the NADA on December 27, 2001 (See 12-27-01 FOI Summary available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm050023.pdf> at 18-19).

You claim that rbGH increases ovulation and embryo survival, and increases the incidence of fraternal twins. And you asserted that, "Because multiple gestations are more prone to complications such as premature delivery, congenital defects and pregnancy-induced hypertension in the mother than singleton pregnancies, the findings of their study suggest that women contemplating pregnancy might consider substituting meat and dairy products with other protein sources, especially in countries that allow growth hormone administration to cattle." The study by Steinman [Reference #60] did not evaluate the effect of rbGH on these factors, but instead reported results of surveys of the diets at conception as recollected by women who had previously given birth to twins or triplets. Your Reference #61 was a press release reporting the results of this same study. The surveys found lower rates of multiple births in women consuming vegan or vegetarian (including milk) diets compared to those eating regular diets that included meat and milk. However, it was not determined whether milk or meat consumed was from rbGH-treated cows. Furthermore, vegetarian women consumed milk and still had low rates of multiple births.

The author of the study suggested that consumption of increased levels of IGF-1 in milk due to rbGH treatment of dairy cows may have increased twinning rates in the U.S. since the 1990s, when rbGH was approved in the U.S. However, as discussed previously, IGF-1 levels in the milk of rbGH-treated dairy cows are well within the normal range of levels found in milk of untreated cows. Furthermore, intestinal absorption of IGF-1 is negligible. Also, the author noted that twinning rates in the U.S. started to increase as early as the 1970s, long before rbGH was approved for use in dairy cows, and were influenced by many other factors, including assisted reproductive technology and delays in childbearing age.

8. The International Ban on the Use and Imports of rbGH Dairy Products.

You claim that “based on the veterinary and public health concerns detailed in this Petition, the use and import of rbGH dairy products has been banned by Canada, 29 European nations, Norway, Switzerland, Japan, New Zealand, and Australia.” In addition, you mentioned that “on June 30, 1999, the Codex Alimentarius Commission, the United Nations Food Safety Agency representing 101 nations worldwide, ruled unanimously not to endorse or set a safety standard for rbGH milk.”

FDA’s decision to approve a drug is based on whether the drug meets the requirements of the FD&C Act. The fact that other countries have or have not approved the same drug is not a consideration.

We note, however, that the 1998 JECFA expert committee concluded that IGF-1 levels in milk of rbGH-supplemented cows do not produce a biologically significant or deleterious effect in people. See JECFA Fiftieth report at 77-78. This conclusion of safety is reinforced by the JECFA decision that an allowable daily intake and maximum residual limits in food are not needed for rbGH and that rbGH can be used without any appreciable risk to the health of consumers. The ruling from the CODEX Alimentarius Commission reflects this 1998 JECFA expert committee recommendation. Report of the Eleventh Session of the CODEX Committee on Residues of Veterinary Drugs in Foods, at 43 (September 15-18, 1998), www.codexalimentarius.org/input/download/report/216/A199_31e.pdf. Furthermore, the 2013 JECFA expert panel reaffirmed this finding. See Seventy-Eighth Meeting at 5. We also note Health Canada’s similar conclusion that “there is no biologically plausible basis on which to conclude that rbST-associated changes in human exposure to IGF-1 will lead to any immune response, change in neonatal intestinal growth and development, or cancer risk in recipients of milk or food products from treated cattle.” Health Canada, “Report of the Royal College of Physicians and Surgeons of Canada Expert Panel on Human safety of RBST” (Jan. 1999), http://www.hc-sc.gc.ca/dhp-mps/vet/issues-enjeux/rbst-stbr/rep_rcpsc-rap_crmcc-eng.php.

9. The FDA Policy on Labeling rbGH Milk.

Finally, you state that FDA misled dairy producers and consumers with regard to a “requirement for labeling of milk from rbGH milk, to the effect that ‘No significant difference has been shown between milk derived from rBST-treated and non-rBST treated cows.’” You cite a July 27, 1994, letter from the (then) Executive Director to the FDA Commissioner to a representative of the State of New York Department of Agriculture and Markets, as stating that “FDA has determined it lacks the basis for requiring such labeling in its statute” to support your proposition that the purported labeling requirement is misleading.

Your argument is flawed for a number of reasons. First, the statement you reference regarding there being no significant difference shown between milk derived from rbGH-treated and non-rbGH treated cows is, by itself, an accurate statement. As

discussed above, after carefully reviewing relevant data and information, the Agency has found, and repeatedly confirmed, that all available scientific evidence demonstrates that there is no significant difference between milk derived from rbGH-treated and non-rbGH-treated cows.

Second, FDA has not required that labeling for milk products bear the statement that you reference. Instead, the Agency explained, in the Interim Guidance, that certain voluntary statements about the use of rbGH in food labeling may be misleading where such statements imply that milk from non-rbGH-treated cows is safer or of higher quality than milk from rbGH-treated cows, and therefore such labeling statements should be put in appropriate context to avoid misleading consumers. The statement you reference was included in the Interim Guidance as an example of accompanying information that helps provide such appropriate context.

Third, your reliance on a quotation from an FDA letter regarding FDA's statutory authority in support of your proposition is misplaced. The quotation refers to FDA's lack of authority to require food labeling indicating that a food was made with milk from cows treated with rbGH where no material difference has been shown between milk from cows treated with rbGH and milk from cows not treated with rbGH. See Stauber v. Shalala, 895 F.Supp. 1178, 1196 (W.D. Wis., 1995) (holding that absent a material difference between milk from cows treated with rbGH and milk from cows not treated from rbGH, FDA does not have a sufficient basis to require labeling of rbGH milk under the FD&C Act).

FDA has the authority to require that food labeling be truthful and not misleading. Under section 403(a)(1) of the FD&C Act, a food is misbranded if its labeling is false or misleading. Both the presence and absence of information in food labeling can be misleading. Section 201(n) of the FD&C Act further defines misleading labeling, particularly with respect to the absence of information in labeling. Under section 201(n), labeling is misleading if it fails to reveal facts that are material in the light of representations made or suggested in the labeling, or material with respect to consequences which may result from the use of the article to which the labeling relates, or under such conditions of use as are customary or usual. FDA has generally interpreted the scope of "materiality" to mean information about the attributes of the food itself. FDA has required special labeling on the basis of it being "material" information in cases where the absence of such information may: (1) pose special health or environmental risks (e.g., warning statement on protein products used in very low calorie diets); (2) mislead the consumer in light of other statements made on the label (e.g., requirement for quantitative nutrient information when certain nutrient content claims are made about a product); or (3) in cases where a consumer may assume that a food, because of its similarity to another food, has nutritional, organoleptic, or functional characteristics of the food it resembles, when in fact it does not (e.g., reduced fat margarine which is not suitable for frying).

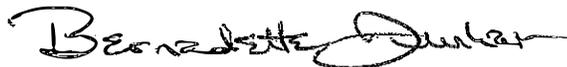
The basis for the statement regarding FDA's statutory authority was, and remains, accurate. While FDA has the authority to require that material information be

included on a food's label, your petition provides no basis upon which to conclude that a material fact has been omitted from the labeling of milk where such milk is produced by cows that have been administered rbGH and the labeling does not disclose such information. Because the Agency has not found that there is a significant difference between milk from cows treated with rbGH and milk from untreated cows, the fact that a food contains milk from cows treated with rbGH is not "material" information that necessitates disclosure in the food's labeling.

Accordingly, FDA has concluded that it does not have the authority to require such labeling for milk from rbGH-treated cows. Similarly, because FDA has found that there is no significant difference between milk from cows treated with rbGH and milk from cows not treated with rbGH, FDA has advised producers, in its Interim Guidance, to provide appropriate context where they voluntarily label their milk products as being produced from cows not treated with rbGH in order to avoid making misleading statements. See Interim Guidance at 6280.

In light of the above, FDA concludes that your petition provides no basis for suspending or withdrawing the approval of the new animal drug application for Posilac or requiring additional labeling of milk or other dairy products produced from the milk of treated cows. FDA has determined that the drug is safe and effective for its intended uses and that there is no significant difference between milk from cows treated with rbGH and untreated cows. Based on those determinations, and for the reasons described in this response, the Petition is denied.

Sincerely,



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