Consumers Union

February 1, 2003

The Honorable G. Steven Rowe
Attorney General
6 State House Station, 6th Floor
Augusta, ME 04333

Re: Petition to Suspend Use of State of Maine Quality Trademark for Milk and Milk Proteins

Dear General Rowe,

I am writing to you after a discussion I had with Marilyn Anderson from the Maine Coop Voices United. She told me of the attempt by Monsanto to force Maine to allow milk from cattle treated with recombinant bovine growth hormone (rbGH) to be eligible for the Maine "Seal" (currently prohibited by present law) and for the Attorney General to legally prosecute dairies that advertise that their milk comes from farmers that pledge not to use milk from rbGH-treated cattle. Since I testified before the Maine legislature when they were hearing the original mandatory labels bills for milk and other dairy products derived from rbGH-treated cattle, I would like to weigh in on a few issues that are used in Monsanto's Petition. I will argue that: milk from rbGH-treated cattle differs from milk from untreated cattle, unanswered questions exist about certain safety issues associated with milk from rbGH-treated cattle, labeling milk as to use of rbGH does not deceive consumers, and FDA does not require a "contextual statement" on milk labeled as coming from cattle not treated with rbGH. In sum, we support the right of Maine to use its Quality Seal in the way that it presently does (i.e. by requiring that 80% of the milk come from dairies in Maine and that farmers pledge not to use rbGH) and urge you to deny Monsanto's Petition. To grant Monsanto's petition would endorse the idea that consumers do not have a right-to-know whether their milk comes from cows that have not been treated with rbGH (or from farmers who pledge not to use rbGH), which we think would be a bad idea.

I. Milk from rbGH-treated cattle differs from milk derived from untreated control cattle

Monsanto attempts to argue that milk from rbGH-treated cattle "is equivalent in all respects to other milk." We disagree. First, Monsanto's rbGH differs from cattle's natural growth hormone. A cow's natural growth hormone is a protein that consists of 190 or 191 amino acids. Monsanto produced a version of the natural bGH which differed by a single amino acid (methionine), which was added to one end of the molecule (the N-terminus). This difference facilitated the production of rbGH by bacteria, e.g. the yield of rbGH produced per bacteria was higher when the gene coded for an rbGH molecule that ended with a methionine than one that did not. Thus, milk from rbGH-treated cattle will contain rbGH, while milk from untreated cattle will not.

Monsanto's rbGH product, POSILAC, which has an extra amino acid (methionine) at one end of the molecule is also more immunogenic (e.g. stimulates the immune systems more) than natural bGH produced by a cow's pituitary gland, e.g. there are differences in how the immune system reacts to a cow's natural bGH and Monsanto's rbGH. A paper published in 1994 using Monsanto's rbGH product, "Identification of antigenic differences of recombinant and pituitary bovine growth hormone using monoclonal antibodies," demonstrated "that small differences in structure, for example through additional N-terminal amino acids, can markedly change the immunogenic characteristics of a protein" (Erhard et al., 1994: pg. 16).

Thus, rbGH differs from cow's natural bGH in ways that can be detected by the immune system. Further, some of the bGH in cow's milk will consist of rbGH; conversely, rbGH will not occur in the milk of untreated cows. So, the presence of rbGH in the milk of cows treated with rbGH constitutes a difference with the milk from untreated cows.

Second, Monsanto's own studies have shown that milk from rbGH-treated cattle has elevated levels of insulin-like growth factor-1 (IGF-1) compared to milk from untreated cattle. IGF-1 is a protein hormone found in the milk of all mammals. In addition, bovine IGF-1 and human IGF-1 are identical (i.e. they have the exact same amino acid sequence). Prior to gaining approval for POSILAC in the fall of 1993, Monsanto submitted a number of studies to the FDA concerning the effect of rbGH on milk levels of IGF-1. There were four studies mentioned in the FDA's Freedom of Information Act summary of the data used to gain approval for POSILAC; the first three of these studies were also discussed in the 1990 paper in *Science*, "Bovine growth hormone: food safety evaluation," authored by two FDA scientists, Judith Juskevich and Greg Guyer (Juskevich and Guyer, 1990). I briefly discuss all four studies below.

The first Monsanto study (Torkelson et al., 1988) involved 18 cows and an rbST dosage of 500 mg injected every 14 days, with milk collected 7 days after

each of 3 injections. The study found that "After each of the 3 doses, mean milk IGF-I in controls was 3.22, 2.62 and 3.78 ng/ml and in treated cows was 3.80, 5.39 and 4.98 ng/ml, respectively. Differences between treated and control groups was [sic] significant after the second and third doses" (FAO, 1993: 121). Thus, the average IGF-I concentrations were increased by 18%, 106% and 31.7% for injection cycles 1, 2, and 3, respectively in the treated groups compared to controls.

The second Monsanto study (White et al., 1989) involved 18 cows and an rbST dosage of 500 mg injected every 14 days, with milk collected 7 days after each of 3 injections. As in the Torkelson et al. study, mean milk IGF-I concentrations were statistically significantly higher after the second and third doses. Mean milk IGF-I in controls was 3.17, 3.34 and 3.35 ng/ml and in treated cows was 3.50, 5.33 and 4.68 ng/ml, respectively. Thus, the average IGF-I concentrations were increased by 10%, 60% and 40% for the first, second and third doses, respectively in the treated group compared to controls.

The third Monsanto study (Miller et al., 1989) involved 64 cows and an rbST dosage of 500 mg injected every 14 days, with milk collected 7 days after each of 10 injections. The study found that "milk concentration of IGF-I was increased across the 10 injection cycles" (FAO, 1993: 126). For primiparous cows (i.e. those giving birth for the first time, aka first calf heifers) the increase was 74%, from 3.5 ng/ml to 6.1 mg/ml for control and rbST-treated cows, respectively. For multiparous cows, the increase was 41%, from 3.9 ng/ml to 5.6 mg/ml for control and rbST-treated cows, respectively. Both results are statistically significant.

The fourth Monsanto study was conducted at the Monsanto Animal Research Center in O'Fallon, Missouri and reported in late 1993 in the US FDA's Freedom of Information Act Summary of the data used to gain approval for POSILAC, Monsanto's rbST product. This study involved 18 cows, an rbST dosage of 500 mg injected every 14 days, with milk collected 7 days after each of three injections. IGF-I levels were statistically significantly elevated in milk from rbST-treated cows. Indeed, the milk IGF-I levels of treated and control cows did not even overlap, i.e. the milk IGF-I level from the 9 rbST-treated cows was higher than any of the levels found in the milk of control cows: "During the study, milk IGF-I concentrations ranged from 3.16 to 3.35 ng/ml for control cows and from 3.49 to 5.31 ng/ml for treated cows. The difference in milk IGF-I between control and treated cows was statistically significant at the 5% probability level" (FDA, 1993: 121).

In sum, all four studies done by Monsanto found statistically significant increases in levels of IGF-1 in milk from rbGH-treated cows compared to milk

from untreated cows. The study by Miller et al. (1989) used the largest number of cattle (64) and had the longest duration of experiment (10 injection cycles or 140 days) and found increases in mastitis of 74% and 41% for primiparous and multiparous cows, respectively. According to label directions, POSILAC can be used starting in the 9th week after lactation and can be used to the end of the lactation cycle. Since a normal lactation period is ten months, this means using about 20 injection cycles. So, Monsanto's own data show that there is a significant increase in IGF-1 levels in milk from rbGH-treated cows compared to milk from untreated cows.

II. Unanswered questions do exist about certain safety issues associated with milk from rbGH-treated cattle

Contrary to Monsanto's and FDA's assertion, there are still certain safety issues associated with milk from rbGH-treated cattle that have still not been fully resolved. The primary unanswered safety question revolves around IGF-1.

The issue of IGF-1 and its potential human health impact was raised by both the National Institutes of Health (NIH) and the American Medical Association (AMA) in the early 1990s just after the paper, "Bovine growth hormone: food safety evaluation," written by FDA scientists and published in *Science* demonstrated that milk from rbGH-treated cows had statistically significantly higher levels of IGF-I compared to milk from untreated cows. The NIH held a Technical Assessment Conference on BST in December 1990. In a statement issued by the NIH Health Expert Committee after the Conference, they stated "Whether the additional amount of insulin-like growth factor 1 in milk from [rbGH-treated] cows has a local effect on the esophagus stomach or intestines is unknown" (NIH, 1991). One of the six recommendations for further research in the report was "Determine the acute and chronic actions of IGF-I, if any, in the upper gastrointestinal tract".

Three months after the NIH conference, in March 1991, the Council on Scientific Affairs on the AMA published a paper in the *Journal of the American Medical Association* entitled "Biotechnology and the American Agriculture Industry." The section that talked about human health impacts of rbGH use stated, "Further studies will be required to determine whether ingestion of higher than normal concentrations of bovine insulin like growth factor is safe for children, adolescents, and adults" (AMA, 1991: 1433).

These warnings of the need for more research on the potential safety implications of IGF-I were very prescient, as discussed below. At the time of these warnings, it was known that, besides its effect on human metabolism, IGF-I

had been associated with the growth of numerous tumors, including colon (Tricoli et al., 1986), smooth muscle (Hoppener et al., 1988), breast (Rosen et al., 1991), and others (Pavelic et al., 1986). A basic question that was not known at the time, however, was whether IGF-I in milk could survive digestion; that's in large part why both the NIH and the AMA called for further research.

The US FDA has maintained that IGF-1 does not survive digestion. Furthermore, FDA argues that even if IGF-1 does survive digestion, the levels in cow's milk (from 1-13 ng/ml) are so low compared to levels in human sera (about 100-200 ng/ml), that there would be no effect on the total serum levels of IGF-1 so there would be no adverse health effect.

We believe the FDA is wrong on both accounts. First, a couple of studies done in the mid-1990s suggest that IGF-I may survive digestion. A rat study, published in 1995, found that IGF-I, in the presence of casein (the major milk protein), easily survived digestion in the stomach, enabling it to pass into the small and large intestine (Xian, et al., 1995). The presence of casein also had some protective effect in the duodenum and dramatically increased the half-life of IGF-I in the intestine. The authors concluded that using casein may make it possible to give therapeutic oral doses of IGF-I: "It can be concluded that IGF-I cannot be expected to retain bioactivity if delivered orally because of rapid proteolysis in the upper gut, but the use of IGF antibodies and casein could represent useful approaches for IGF-I protection in oral formulae" (Xian et al., 1995: 215). Another rat study done in 1997 clearly demonstrated significant gastrointestinal absorption of recombinant human IGF-I (rhIGF-I) (remember that human IGF-1 and bovine IGF-1 are identical). After oral administration of rhIGF-I at the dose of 1.0 mg/kg body weight (half the dosage that FDA found to be completely digested and not orally active), the study "found that a considerable amount of rhIGF-I was absorbed into the systemic circulation and that the bioavailability was 9.3%. . . . The coadministration of aprotinin and that of casein enhanced the bioavailability further: 46.9% and 67.0%, respectively" (Kimura et al., 1997: 611). Since determination of the blood levels of a protein can be a bit tricky (various methods have their advantages and drawbacks), the authors used three analytical methods. All three methods clearly showed that both casein and aprotinin lead to statistically significant increases in absorption of IGF-I. The authors concluded that "[t]hese results strongly support the feasibility of the p.o. [peri oral] administration of rhIGF-I" for therapeutic purposes in humans (Kimura et al., 1997: 618). This paper clearly showed that IGF-1 can survive digestion when in the presence of casein, the major protein in milk.

Second, and more important, a series of papers published in the late 1990s and as late as 2002 have found higher levels of serum IGF-1 to be associated with

increased risk of a number of cancers, especially prostate (Chan et al., 1998a; Harman et al., 2000), colon (Ma et al., 1999; Giovannucci et al., 2000), lung (Yu et al., 1999) and premenopausal breast cancer (Toniolo et al., 2000). Indeed, a paper ("Role of the insulin-like growth factor family in cancer development and progression") published in the *Journal of the National Cancer Institute* in 2000 laid out a biological mechanism to explain the link between IGF-1 and cancer (Yu and Rohan, 2000).

As for the argument that levels of IGF-1 in milk are too low to alter concentrations of IGF-1 in human serum and so there could be no health effect of the increased levels of IGF-1 in milk from rbGH-treated cattle, a paper published just last fall shows this argument may be incorrect as well. A team of scientists at Brigham and Women's Hospital and Harvard Medical School in Boston used data from a large, long-term (25 years) study of more than 1,000 nurses who record their diets carefully and who were then watched for changes in health. The study found that higher serum levels of IGF-I were found in the women who consumed the most dairy products and noted that other studies had found a link between increased dairy intake and increased serum IGF-I levels. As the study noted: "Our most consistent dietary finding was the positive association of IGF-I levels with total dairy and milk intake. . . Two other studies have supported an effect of milk intake on IGF-I levels. A randomized trial of 204 men and women where the intervention was to encourage consumption of three servings/day of nonfat milk to affect bone remodeling found that the 101 subjects in the intervention group had a statistically significant 10% average increase in serum IGF-I levels, whereas the control group had no change in levels (Heaney et al., 1999). In addition, Ma *et al.* (2001) observed a positive association between intake of dairy food and IGF-I levels among 318 men enrolled in the Physicians' Health Study. . . . *These results raise the possibility that milk consumption could influence cancer risk by a mechanism involving IGF-I*. In fact, positive associations between milk intake and risk of prostate cancer have been reported (Chan et al., 1998b; Talamini et al., 1986; Tzonou et al., 1999; La Vecchia et al., 1991; Talamini et al., 1992; and Schuurman et al., 1999). In the NHS, one or more servings of milk/day was associated with a higher risk of serous (sic) ovarian cancer (relative risk, 1.66; 95% confidence interval, 1.10 - 2.51) compared with three or fewer servings/month (Fairfield et al., 2000)" italic added (Holmes et al., 2002: pp. 859-860). A copy of this paper is appended to this letter.

A Reuters new story about this new study (copy attached), issued on September 10, 2002, quoted the lead author on the study, Dr. Michelle Holmes, discussing how this research suggests that IGF-I can be associated with various cancers: "Pregnancy may lower a woman's risk of cancer but drinking milk could raise it, researchers reported on Tuesday. . . . This is the first study to report that the more pregnancies a woman had, the lower was her blood level of

IGF-1, Holmes said. 'Pregnancy is known to protect against several cancers such as breast and colon cancer. It is possible that the mechanism of this protection could be through lowering IGF-1 levels.' . . . 'We concluded that greater milk consumption was associated with higher levels of IGF-1,' said Holmes. '*This association raises the possibility that diet could increase cancer risk by increasing levels of IGF-1 in the blood stream. However, more research must be done to determine whether milk consumption itself is directly linked to cancer risk*' " italics added (Reuters, 2002).

All this new research on IGF-I published in the late 1990s and early 2000s —its connection with various cancers, its ability to potentially survive digestion when in milk, and the connection between increased milk consumption and increased sera levels of IGF-I—clearly show that there are still unanswered health questions associated with the consumption of milk from rbGH-treated cows. Clearly, more research into this area needs to be done to answer the questions raised by the new research described above.

III. Labeling milk as to use of rbGH does not deceive consumers

In their Petition, Monsanto tries to argue that any mention in an advertisement as to whether milk comes from non-rbGH-treated cattle "deceives consumers." We strongly disagree with these assertions. We note that the advertisements from Oakhurst Dairy and from H.P. Hood that Monsanto refers to clearly state that the farmers pledge not to use rbGH; the ads do not claim that their farmers absolutely don't use rbGH. Such a claim is truthful because all the farmers do sign affadavits that they do not use rbGH on their cattle.

Monsanto also argues that the ads "mislead consumers by creating the false impression that milk is somehow better if it is produced without the use of rBST. Indeed, these claims falsely suggest that there are health or safety risks associated with milk from rBST-supplemented cows." We do not necessarily believe that a truthful label—such as "from farms that pledge not to use artificial growth hormone" or "Our Farmers' Pledge: No Artificial Growth Hormones"—always leads to the conclusion that milk from cows not treated with artificial growth hormones is "safer or superior to non-supplemented milk." While some consumers may draw such a conclusion from these ads, others may not. Indeed, if such labels are considered to mislead consumers, then, by the same logic, labels such as "contains no artificial flavoring or colorings" or "contains no preservatives" would also be considered to mislead consumers. Yet no one has suggested that such labels should be banned.

Finally, we are concerned with Monsanto's "request that the Attorney General initiate law enforcement proceedings to challenge deceptive claims in

the marketplace." Such legal proceedings against truthful claims would only serve to chill commercial free speech in this area and would make it virtually impossible for dairy chains to label or advertise milk as to whether it comes from farmers who have pledged not to use rbGH on their cows. The end result would be that consumers may be denied a choice about whether the milk they drink comes from cows that have been treated with rbGH or not. We strongly support a consumers right-to-choose in this area and so ask that you not initiate any legal proceeding against Oakhurst Dairy and H.P. Hood.

IV. FDA does not require a "contextual statement" on milk labeled as coming from cattle not treated with rbGH

In their Petition, Monsanto suggests that a "qualifying statement," such as suggested FDA wording "No significant difference has been shown between milk derived from rbST-treated and non-rbST treated cows," would be needed "to qualify the misleading claims conveyed by the quality Seal or the labels and advertisements." We strongly disagree with the notion that such "qualifying statements" are needed or required. First, we note that the suggested FDA language is misleading, because differences between milk from rbST-treated and non-rbST treated cows—particularly the statistically significant increases in IGF-I and the presence of rbGH—have been found. Second, the FDA has clearly stated that such a qualifying or "contextual" statement is not required at all. A letter written to Harold Rudnick (Director of the Division of Milk Control in the State of New York Department of Agriculture and Markets) by Jerry Mande (Executive Assistant to then FDA Commissioner David Kessler) and dated July 27, 1994, clearly shows this: "as I indicated, the bottom line is that a contextual statement is not required, that in many instances a statement like 'from cows not treated with rbST' would not be misleading and in no instance is the specific statement 'No significant difference. . .' required by FDA. . . . the intent of our guidance was to have a uniform voluntary rbST labeling regime among states, that states were not necessarily pre-empted from developing alternative programs. For example, a state that has right-to-know would not be pre-empted by FDA from requiring rbST labeling even though FDA has determined it lacks the basis for requiring such labeling in its statute" (Mande, 1994: 2) (a copy of the letter is included as an attachment to this letter).

In sum, FDA has clearly stated that a "contextual statement" is not required milk labeled as coming from cows not treated with rbGH. In fact, I would argue that Maine's Quality Seal program would constitute such an "alternative program" as discussed in the FDA letter above and so would be perfectly legal. Finally, it should be noted that the Quality Seal program is a voluntary and not a mandatory label.

In conclusion, for all the reasons discussed above, we urge you to deny Monsanto's Petition.

Sincerely,

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