Forum

Recombinant bovine somatotropin and animal welfare

David S. Kronfeld, PhD, DSc, MVSc, DACVN, DACVIM

In November 1998, an expert panel appointed by the **Canadian VMA (CVMA)** at the request of Health Canada, but working independently, found "a number of legitimate animal welfare concerns associated with the use of **rBST**" **(recombinant bovine somatrotopin)**.[1] These included an increased risk of clinical mastitis and lameness, and a reduction in the lifespan of treated cows. The panel presented meta-analyses with brief discussion about epidemiologic factors. It concluded that "current health practices. . . were inadequate to eliminate the increased risk of clinical mastitis and lameness." This report delayed approval of an rBST drug intended to increase the production of marketable milk.

In March 1999, a working group from within the Scientific Committee on Animal Health and Animal Welfare of the European Commission presented a more extensive report that summarized similar results and engaged in substantive discussion of animal welfare from the points of view of physiologists and epidemiologists.[2] It concluded that rBST should not be used in dairy cattle. In October 1999, the European Commission banned the use and marketing of rBST in the European Union as of Jan 1, 2000.

In contrast, the US FDA approved a rBST drug in 1993. A major stumbling block was the increased incidence of clinical mastitis associated with the use of rBST, as revealed at a public meeting of the FDA's Veterinary Medical Advisory Committee in March 1993.[3-5,a-c] In the 8 pivotal trials (487 cows) that served as the main basis for the mastitis decision, overall relative risk of cows with signs of mastitis was 1.79 (P = 0.001).[3] The FDA[a] rejected the proposal of a company scientist that this result was unobjectionable (by analogy with genetic improvement), because it was accounted for by an increase in milk production.[6,b] It accepted, however, the contention of a company consultant[c] that rBST-associated mastitis was 4 to 9 times less than variation attributable to parity, lactational stage, season, and herd, thus was not a public health concern with respect to antibiotic residues in milk.[3]

The **Freedom of Information (FOI)** Summary for Posilac[3] does not mention animal welfare, but Dr. Gerald B. Guest, Director of the FDA's Center for Veterinary Medicine, raised the issue of humaneness at the March 1993 meeting. He said "the amount of mastitis. . .seems to be manageable. . .not to be over burdensome or stressful to the animal."[4] The FDA subsequently allowed the company to claim that rbST-associated mastitis is a "small increase [that] has little practical or biological significance when compared with other herd factors such as season, parity, herd or stage of lactation" and to imply in the drug's labeling that it is manageable in regard to animal health.[6,7]

In this article I aim to identify and clarify reasons for the different decisions made in the in the United States, Canada, and Europe, with regard to use of rbST in dairy cattle.

Pertinent differences concern the laws and ethical constraints, data analyzed, neglect or observance of epidemiologic principles, and interactions with public policies. Emphasis will be placed on mastitis, because this disease is important clinically and economically, and in regard to milk quality, public health, and animal welfare.

Laws and Ethical Issues

Canada has a code of practice for the care and handling of dairy cows that includes the prevention of injury and disease.[1] The United States has no comparable statute. The US Federal Animal Welfare Act deals with the use of farm animals for teaching and research but not for production. State and county laws about cruelty to animals mainly concern the welfare of animals kept as companions and rarely are applied to animals raised for food production. Several European countries have laws or regulations directly concerning the welfare of farm animals. The United Kingdom's Five Freedoms, for example, includes freedom from suffering, injury, and disease caused deliberately by farming practices.[8]

Ethically, veterinarians in the United States may be guided by the Veterinarian's Oath (adopted by the AVMA in 1969) to benefit society "through the protection of animal health, (and) the relief of animal suffering." Similarly, the Code of Ethics of the American Registry of Professional Animal Scientists states that an animal scientist will "have proper regard for the safety, health, environment and comfort of animals."[9] Although veterinarians had a supervisory role, the FDA's primary decision on rBST and its adverse effects was made by its Biometrics and Production Drug Division, staffed primarily by animal production scien-

From the Departments of Animal and Poultry Sciences and Large Animal Clinical Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061–0306.

tists. In Canada, the decision was made predominantly by veterinarians with extra training in epidemiology and preventive medicine. The European group consisted of veterinary epidemiologists and physiologists expert in animal welfare.

The FDA is required to evaluate only 3 scientific and technical points: 1) a drug's specifically claimed efficacy; 2) its general safety for the target animal, human consumers, and the environment; and 3) its manufacture. The CVMA panel was asked whether serious health problems could be adequately controlled by current management practices.[1] The European group was also charged with evaluating animal welfare within a broad social context,[2] sometimes called a fourth hurdle. The influence of social values and public policy is explicit only in the European fourth hurdle, but should not be assumed absent from the Canadian and American decision making.

Data Analysis

The FDA first analyzed data from carefully monitored pivotal trials on institutional herds, for example, 5 for efficacy and 8 for mastitis.[3] It subsequently analyzed 28 trials, including 10 monitored in the **postapproval monitoring program (PAMP)**, that used commercial herds. The PAMP data were released at a public meeting of the FDA in November 1996,[d] and some have been published.[2,10]

Regarding clinical mastitis, the overall relative increase in incidence associated with rBST use was 79% in the institutional trials and 23% in the commercial herds.[2,3] Mean mastitis incidence was about the same in both sets of rBST groups, but it was higher in control groups in the commercial herds.

The Canadian panel applied meta-analyses to 2 sets of data, those submitted by Monsanto, and other sets of data for similar rBST-drugs from other companies,[1] which differed only in extra amino acids that linked the bovine gene to the bacterial ribosome during manufacture.[5] In regard to clinical mastitis, data from 18 Monsanto trials were supplemented by data from another 11 trials of other companies. The relative increases were 24 and 27% for incidence rate (cases/cow) for all companies and Monsanto only, respectively, with corresponding values of 27 and 29% for mastitis risk (affected cows/cows at risk). The panel settled for an overall approximation of 25%. An FDA spokesperson was reported to say that "the Canadian figures are based on trials involving several products, often given at different frequencies and at several dosages—some dosages far exceeded the expected use level."[11] In my opinion, this statement represents part of the truth but is misleading, because rBST-associated mastitis was slightly higher, as noted above, for the Monsanto data than for all products.

The European review was comprehensive, but included little new data analyses.[2] It cited results of previous meta-analyses that indicated relative increases of 14 to 47, 23, 25 (actually 24 to 29), 42, and 79% in the incidence of clinical mastitis associated with the use of rBST. Further data analyses were hardly necessary, because "these estimates describe an increase (in mastitis incidence) which is not only statistically significant but also biologically relevant and of considerable welfare concern."[2]

Lameness was not increased by rBST in 12 pivotal preapproval trials despite several foot and limb problems reported by Monsanto and the FDA.[3,7] In contrast, lameness was increased by about 50% according to the Canadian meta-analyses,[1] by 2.1 in terms of days affected, and by 2.2 for multiparous cows affected according to the European analysis of the PAMP data.[2] In the PAMP, lameness was associated mainly with laminitis, which was associated with increased feeding of grain.[10] This practice was intended to maintain body condition and reduce the risk of mastitis.[e]

Reproductive inefficiency (mainly reduced pregnancy rate and increased days not pregnant) was recognized by the FDA.[3] The regulatory agency allowed the labeling recommendation of a reproductive management program. Canadian meta-analyses revealed a 40% relative increase in nonpregnancy rate, which would contribute to an increased culling rate.[1] Even larger relative increases in nonpregnancy rate were found in the European review[2]: 10 and 37% of primiparous cows in control and treated groups, respectively, with corresponding numbers of 18 and 27% in multiparous cows. An increased culling rate or shorter milking life would affect metabolic and economic efficiencies.

Epidemiologic Evaluation

The most salient finding in regard to animal welfare was agreed upon by all 3 groups[1-3]: an increased risk of clinical mastitis in cows treated with the rBST drug. In my opinion, this finding was belittled by Monsanto and the FDA,[3,6,b,c] which claimed that the increased risk of developing clinical mastitis during rBST administration is small, compared with other sources of variation, as observed in 3 non-rBST studies,[12-14] and, therefore, manageable in regard to cow health.[6,7,15] I believe this contention should be rejected for several epidemiologic reasons:

- Criteria for diagnosis of a case of clinical mastitis were not consistent from study to study.[12-14] A new case required a prior infection-free period of 14 or 21 days. Infection of 2 quarters represented 1 or 2 cases. Isolation of 2 bacterial species from 1 quarter was counted as 1 or 2 cases.
- The mastitis data from the rBST trials were adjusted for milk production or placed on a milk yield basis.[15,a,c] Comparable adjustments for milk production in the reference trials[12-14] would have reduced the effects of lactational stage or herd-to-herd variation by a factor of 2 or more.
- The rBST data were diluted ($\times$ 0.8) from the administration period (8 months) to the whole lactation (10 months), despite the concentration of most of the extra mastitis into the first 6 weeks of administration.[d]
- The claim that the increased risk of mastitis in rBST herds is less than differences in incidence found between seasons would call for a statistical test, but no such test was presented.[15,a,c]
- Discrimination was not made between controllable and uncontrollable sources of variation. The claim

that rBST-associated mastitis is manageable because it is less than seasonal variation is a nonsequitor, because we cannot control the weather.

- Notice was not taken of catabolic stress, which is associated with the high incidence of mastitis in the first 2 months of lactation and during the first 2 months of rBST administration.[5] Body tissue utilization, that is, loss of body fat and protein, accounts for the extra milk during the first 2 months of rBST administration, and rBST-associated mastitis develops primarily in the first 6 weeks of administration[d] in association with loss of body condition.[e]
- Averaging obscured the influence of mastitis management evident in the 8 pivotal trials.[a] If mastitis incidence in control groups is taken to reflect mastitis management, then the trials can be stratified into 2 groups, one with poor management (control incidence > 25%), the other with good management (control incidence < 10%). In 7 groups (3 primiparous and 4 multiparous) with poor management, rBST treatment had little or no effect on incidence of mastitis. In 9 groups (5 primiparous and 4 multiparous) with good management, rBST treatment had no effect in 1, but resulted in large increases (absolute and relative) in 8.[5] This difference (0/7 vs 8/9) is significant ($P = 0.0014$). Clearly, good management of mastitis in the absence of the drug failed to reduce and evidently exacerbated the mastitic effect of rBST.
- Notice was not taken of drug resistant bacteria, notably *Staphylococcus aureus*, which have been associated with mastitis during rBST administration.[16-18] Extensive extralabel use of antibiotics (piperacillin, gentamicin, and trimethoprim-sulfonamide) was reported in a company trial.[5,18] In 3 trials, the number of days the cows were treated was consistently higher in rBST-treated groups than in controls.[5] In the 8 pivotal trials, mean days affected were 1.49 and 2.15 ($P < 0.0001$) in multiparous cows.[3]

For these 8 reasons and others,[4] I believe the FDA should have rejected the company's management assumption regarding clinical mastitis and cow health. Instead, the management assumption's acceptance enabled approval of the rBST drug despite the extra mastitis and 20 other adverse effects listed on the package insert. Nine adverse effects may be regarded as painful and disabling disorders,[10] which brings up the animal welfare issue. Only 5 (on my count) adverse effects were reported in the hundreds of papers written by the company's scientists and consulting professors,[10,19,20] which brings up another ethical issue—the lack of timely and candid disclosure of adverse health effects.[21]

Public Policies

From 1984 to 1994, rBST was portrayed in the scientific literature as a harmless hormone that had a homeorhetic (chronic regulatory) action on nutrient partitioning and metabolism. In this view, all of rBST numerous effects were exquisitely coordinated to improve milk production[22] Adverse effects were consistently denied, and their absence was taken to confirm the homeorhetic theory. An example was a difference in incidence of mastitis, 4 of 40 in the control group, compared with 14 of 40 in the rBST-treated group (relative risk 3.5, $P = 0.015$).[6,10,23,a] The authors reported[22]: "[n]o adverse health effects were observed. . . [a]nimals were in good health throughout the study." This mischaracterization achieved historic importance when numerous subsequent reports of rBST trials consistently followed its example.

In the United States, public policy was forged on the basis of a scientific literature that repeatedly denied observation of rBST's adverse effects,[19,20,24,25] which were subsequently disclosed by the FDA and in the drug's labeling.[3,7,15] In 1987, the USDA made a thorough economic analysis and strongly recommended the prompt approval of rBST to enable US farmers to compete in a global economy.[24] In 1991, the US Senate's Office of Technology Assessment stated,[20] "[c]atastrophic effects such as . . . mastitis . . . have been postulated to occur with (rBST). However, no such effects have been observed . . . in any scientifically valid studies, nor have subtler effects been in evidence." The folly of this claim was revealed later in the drug's labeling,[3,7,15] but the unreserved commendation of rBST by the US Senate's Office of Technology Assessment testified (obviously in an unintended way) to the effectiveness of delayed disclosure of the drug's adverse effects in shaping public policy.

In contrast to reports on rBST, reports of adverse effects of rPST in pigs were timely and candid.[26,27] Safety concerns—lameness, poor bone mineralization, osteochondritis dissecans of joints, and gastric ulcers—chilled the development of rPST as a drug. By analogy, if the observation of rBST-associated mastitis had been disclosed in 1988–1989 instead of being denied,[22] development of public policy surely would have dampened and jeopardized approval of the rBST drug.

The drug's approval was enabled, in part, by the FDA's acceptance of the assumption that the drug's adverse effects on cow health were manageable by current practices. The FDA's 1993 decision was contrary to the data, as reviewed in this article, but compliant with US public policy that strongly favored approval of the drug.[20,24,25]

The political climate in Canada was shaken by revelations of alleged attempts by an rBST manufacturer to influence Health Canada. An expert panel was chosen by the CVMA. It suggested that the manufacturer should be required to do further studies to substantiate the effectiveness of health management practices. This cautious suggestion is in tune with numerous doubts raised in the 1998–1999 senate hearings in Canada.

The negative European decision on rBST also is clearly in line with public policies that seriously address animal welfare. Chapters on the characterization of animal welfare, on the status of highly productive cows kept in confinement, and on the extra effects of rBST illuminate the interplay between moral values and scientific evidence in decision-making.[2]

The initial reaction of the FDA to contrary decisions has been to defend its approval of the rBSTdrug.[11] An internal review is underway and, if history repeats itself, will weigh public policy regarding US leadership

in biotechnology and competitiveness in a global economy[20,24,25,28] against physiologic and epidemiologic assessments of animal welfare.[1,2]

[a]Condon RJ. Presentation at a public meeting of the Veterinary Medical Advisory Committee, Rockville, Md, March 1993.
[b]Collier RJ. Presentation at the FDA meeting, Rockville, Md, March 1993.
[c]Smith KL. Presentation at the FDA meeting, Rockville, Md, March 1993.
[d]Condon RJ. Presentation at a public meeting of the Veterinary Medical Advisory Committee, Gaithersburg, Md, November 1996.
[e]Cattell MB. Presentation at the FDA meeting, Gaithersburg, Md, November 1996.

References

1. Doohoo I, DesCoteaux L, Dowling P, et al. *Report of the Canadian Veterinary Medical Association expert panel on rBST.* URL: http://www.hc-sc.gc.ca/english/archives.rbst/animals/. Accessed November 1998.

2. Broom D, Dantzer R, Willeburg P, et al. *Report of the Scientific Committee on Animal Health and Animal Welfare on Animal Welfare Aspects of the Use of Bovine Somatotrophin (Adopted 10 March 1999).* URL: http://europa.eu.int/comm/dg24/health/sc/scah/out21_en.html. Accessed March 1999.

3. *Freedom of information summary for Posilac*. Food and Drug Administration, 1993.

4. Kronfeld DS. Concerns about bovine somatotropin. *J Am Vet Med Assoc* 1993;203:190–192.

5. Kronfeld DS. Health management of dairy herds treated with bovine somatotropin. *J Am Vet Med Assoc* 1994;204:116–130.

6. White TC, Madsen KS, Hintz RL et al. Clinical mastitis in cows treated with sometribove (recombinant bovine somatotropin) and its relationship to milk yield. *J Dairy Sci* 1994;77:2249–2260.

7. *Technical manual for Posilac* (revised). St Louis: Monsanto Co, 1994.

8. Farm Animal Welfare Council. *Second report on priorities for research and development in farm animal welfare*. Tolworth, UK: Ministry of Agriculture, Food and Fisheries, 1993.

9. *Handbook for Officers, Committees and Representatives of the American Registry of Professional Animal Scientists*. URL: http://www.12.24.208.135/memscv/handbk.html.

10. Kronfeld DS. Recombinant bovine somatotropin: synpunkter pa informations och djurhalsoetik (ethics of communication and animal welfare). *Svensk Veterinartidning* 1997;49:157–165,503–504.

11. Nolen S. US and Canada draw different conclusions on rBST. *J Am Vet Med Assoc* 1999;214:985–986.

12. Smith KL, Todhunter DA, Schoenberger PS. Environmental mastitis: cause, prevalence, prevention. *J Dairy Sci* 1985;68: 1531–1553.

13. Morse D, DeLorenzo MA, Wilcox CJ, et al. Climatic effects on occurrence of clinical mastitis. *J Dairy Sci* 1988;71:848–853.

14. Hogan JS, Smith KL, Hoblet KH, et al. Field survey of clinical mastitis in low somatic cell count herds. *J Dairy Sci* 1989;72:1547–1556.

15. *Technical manual for Posilac*. St Louis: Monsanto Co, 1993.

16. Cole WJ, Eppard PJ, Boysen BG, et al. Response of dairy cows to high doses of a sustained-release bovine somatotropin. 2. Health and reproduction. *J Dairy Sci* 1992;75:111–123.

17. Pell AN, Tsang DS, Howlett BA, et al. Effects of a prolonged-release formulation of Sometribove (*n*-methionyl bovine somatotropin) on Jersey cows. *J Dairy Sci* 1992;75:3416–3431.

18. Eppard PJ, Lanza GM, Hammond BG, et al. *Toxicity of CP115099 in a prolonged release system in lactating cows*. Report MSL 6345. St Louis: Monsanto Agricultural Co, 1987.

19. Bauman DE. Bovine somatotropin: review of an emerging technology. *J Dairy Sci* 1992;75:3432–3451.

20. US Senate Office of Technology Assessment. *US dairy industry at a crossroad: biotechnology and policy choices*. Washington, DC: US Government Printing Office, 1991.

21. Kronfeld DS. Biologic and economic risks associated with use of recombinant bovine somatotropin. *J Am Vet Med Assoc* 1988; 192:1693–1696.

22. Bauman DE, Hard DL, Crooker BA, et al. Long-term evaluation of a prolonged-release formulation of N-methionyl bovine somatotropin in lactating dairy cows. *J Dairy Sci* 1989;72:642–651.

23. Peel CJ, Eppard PJ, Hard DL. Evaluation of sometribove (methionyl bovine somatotropin) in toxicology and clinical trials in Europe and the United States. In: Heap RB, Prosser CG, Llamming GE, eds. *Biotechnology in growth regulation*. London: Butterworths, 1988;107–113.

24. Fallert R, McGuckin T, Betts C, et al. *BST and the dairy industry: a national, regional and farm-level analysis*. Agriculture economic report No. 679. Washington, DC: USDA, 1987.

25. US Senate Office of Technology Assessment. *Technology, public policy, and the changing structure of agriculture*. Washington, DC: US Government Printing Office, 1986.

26. Evock CM, Etherton TD, Chung CS, et al. Pituitary porcine growth hormone (pGH) and a recombinant pGH analog stimulate pig growth performance in a similar manner. *J Anim Sci* 1988;66: 1928–1941.

27. Simonsen HB. PST treatment and leg disorders in growing swine. *Livestock Prod Sci* 1993;36:67–70.

28. Executive Branch. *Use of bovine somatotropin (BST) in the United States: its potential effects*. Washington, DC: US Government Printing Office, 1994.