Bovine Somatotropin (bST) – Possible Increased Use of Antibiotics to Treat Mastitis in Cows, October 30, 2013

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The following report was submitted by FDA's Center for Veterinary Medicine for consideration in the re-evaluation of bovine somatotropin at the seventy-eighth meeting on residues of veterinary drugs by the Joint FAO/WHO Expert Committee (JECFA) on Food Additives, held November 5-14, 2013

BACKGROUND

The United States Food and Drug Administration (FDA) approved a formulation of recombinant bovine growth hormone (bST) in 1993, sometribove zinc, for administration to lactating dairy cows to increase milk production. The FDA concluded that use of the drug increased the risk of clinical mastitis in treated cows, and that it may also increase milk somatic cell count[1]. Approved labeling for the product communicates these risks. These conclusions were reconfirmed in 2003 when the FDA approved a supplemental application for this bST product following reanalysis by the sponsor of the original data and new, post-approval monitoring program (PAMP) data using more accurate mixed-model analyses, not available at the time of the original approval[2].

At the time of the original approval, FDA concluded that the increase in clinical mastitis in sometribove-treated cows was not a public health concern in terms of antibiotic residues in milk being increased above tolerance due to therapeutic treatment of mastitis[1]. When examined on a per unit milk basis, the increase in the incidence of clinical mastitis due to sometribove (approximately 0.1 case per cow per year) was about 4 to 9 times less than the effects due to other sources of variation, such as season, parity, stage of lactation, and herd-to-herd variation. The FDA also noted that there was no indication that these cases of mastitis were more difficult to treat, as reflected by the similar average duration of cases between treated and control cows. The FDA also considered that therapeutic drugs, such as antibiotics for the treatment of clinical mastitis, are to be used in food-producing animals only under approved conditions and with appropriate withdrawal periods (as established by FDA) to ensure that food products are safe for human consumption. State and Federal regulatory bodies monitor milk supplies for drug residues, and any milk that contains illegal residues is discarded. FDA's Veterinary Medicine Advisory Committee and expert consultants confirmed these findings in an open public hearing on March 31, 1993[1].

The Joint FAO/WHO Expert Committee on Food Additives in 1998 evaluated one aspect of the PAMP for sometribove that monitored the percent of milk discarded in the U.S. because

of drug residues above the allowed limit in key dairy states[3]. The PAMP was initiated by the U.S. FDA at the time sometribove was approved (in November 1993) and became commercially available (in February 1994). The objectives of the PAMP were to determine whether the incidence of mastitis in dairy cows and antibiotic use was manageable under actual conditions of use in the U.S. and whether the labeling of the product was adequate. The results of milk monitoring for the two years before commercial use of sometribove (1992-93) were compared with those for the two years after its launch on the market (1994-95). Residues in milk were traced according to the U.S. National Drug Residue Milk Monitoring Program in which the contents of all milk tanker trucks are sampled routinely. The data set represented more than 50% of the total U.S. milk supply. These reports indicated that there was no product-related increase in residues above the approved limit after commercialization of sometribove and that the use of sometribove would have no effect on the safety of milk and dairy products due to violative drug residues resulting from a slightly higher rate of medication of bST-treated animals.

EVALUATION OF DRUG RESIDUE DATA IN THE U.S. MILK SUPPLY

Sometribove has been commercially available in the U.S. for 19 years. The U.S. dairy industry has undergone significant transition during this period. The U.S. Department of Agriculture (USDA) has monitored some of these changes through its National Animal Health Monitoring System (NAHMS) program, conducted by the USDA's Animal and Plant Health Inspection Service. Furthermore, the National Milk Drug Residue Data Base, which provided data on violative drug residues in the U.S. milk supply for JECFA's 1998 evaluation of the sometribove PAMP, continues to monitor and report drug residue information.

These two databases provide updated information on changes and current status of the production of milk in the U.S. They also provide insight on mastitis incidence and antibiotic residues in milk during the period in which sometribove has been commercially available.

U.S. Dairy Industry Demographics: USDA NAHMS Studies

The NAHMS Studies summarize information gathered through surveys conducted by state and Federal agencies, animal health officials, and university researchers and extension personnel. Dairy reports were issued in 1996, 2002, and 2007, and a Dairy Heifer Project was reported in 1991[4]. The reports were based on surveys conducted in major dairy states, typically covering over 75% of U.S. dairy operations.

The NAHMS 2007 Dairy Report provided the number of dairy operations, average number of milk cows, and average milk yield per cow per year in the U.S. from 1991-2006 (see Table 1).

Table 1. U.S. Dairy Industry Demographics, 1991-2006.

Year	Number Dairy Operations	Avg. number of dairy cows	Milk yield (pounds per cow per year)	Total U.S. Milk Production (in million pounds)
1991	180,640	9,826,000	15,031	147,697
1992	170,500	9,688,000	15,570	150,847
1993	157,150	9,581,000	15,722	150,636
1994	148,140	9,494,000	16,179	153,602
1995	139,670	9,466,000	16,405	155,292
1996	130,980	9,372,000	16,433	154,006
1997	123,700	9,252,000	16,871	156,091
1998	117,145	9,151,000	17,185	157,262
1999	110,855	9,153,000	17,763	162,589
2000	105,055	9,199,000	18,197	167,393
2001	97,460	9,103,000	18,162	165,332
2002	91,240	9,139,000	18,608	170,063
2003	86,360	9,083,000	18,760	170,394
2004	81,520	9,012,000	18,967	170,934
2005	78,300	9,043,000	19,565	176,929
2006	75,140	9,112,000	19,951	181,798

Source: NAHMS Dairy Studies. Dairy 2007 Part II: Changes in the U.S. Dairy Cattle Industry, 1991-2007[5]; pages 8, 12, and 14.

The number of dairy operations in the U.S. has declined every year during this period, showing a dramatic 58% overall reduction. This trend was obvious even before 1994 when sometribove was first available commercially. More recent USDA data show that this pattern continues, with an estimate of 65,000 operations existing in 2009[6].

The total number of dairy cows producing milk in the U.S. declined from 1991 to 1998, with numbers tending to stabilize in subsequent years (Table 1). Average annual milk yield per cow increased nearly 33% from 1991 to 2006, however, such that overall U.S. production of milk increased 23% during this period. This trend has continued, with total U.S. production at 189,320 million pounds in 2009[6].

The 2007 NAHMS Dairy study also revealed that the percentage of dairy farm operations with fewer than 50 cows has decreased since 1991, whereas the percentage of operations with more than 100 head has increased every year since 1991. About 11.5% of operations had more than 100 cows in 1991 compared to about 23.3% in 2006 (NAHMS Dairy Study 2007, Part II[5], page 10). The number of operations with 500 or more head has increased. Since 2001, the number of operations with 500 or more dairy cows increased by 20%, from 2795 to 3350. These larger operations also have increased in their share of the inventory of U.S. dairy cows (56 vs. 35% in 2009 vs. 2001) and total milk production (60 vs. 39% in 2009 vs. 2001)[6].

Use of Bovine Somatotropin

The NAHMS survey found that the usage of bST on U.S. dairy operations increased from 9.4% in 1996 to 15.2% in 2002, where it remained in 2007 (Table 2). Percentage of cows treated with bST also increased from 10.1% in 1996 to 22.3% in 2002, followed by a decrease to 17.2% in 2007 (Table 3). Operations with 500 or more milk cows had the largest usage rates each year.

Table 2. Percent U.S. Dairy Operations using bST.

Herd Size (Number dairy cows)	1996	2002	2007
All operations	*9.4 (0.6)	15.2 (0.8)	15.2 (0.8)
Small (<100)	6.5 (0.6)	8.8 (0.8)	9.1 (0.9)
Medium (100-499)	21.0 (1.7)	32.2 (1.9)	28.8 (2.0)
Large (>499)	38.7 (3.9)	54.4 (2.6)	42.7 (2.5)

*Percent (standard error) of cow inventory on January 1 of that year

Source: NAHMS Dairy Studies. Dairy 2007 Part II: Changes in the U.S. Dairy Cattle Industry, 1991-2007[5]; page 73.

Table 3. Percent U.S. Dairy Cows given bST.

Herd Size (Number dairy cows)	1996	2002	2007
All operations	*10.1 (0.7)	22.3 (0.8)	17.2 (0.8)
Small (<100)	3.7 (0.4)	6.2 (0.7)	6.2 (0.7)
Medium (100-499)	13.2 (1.3)	24.5 (1.5)	17.7 (1.4)
Large (>499)	17.9 (2.3)	34.1 (1.8)	22.6 (1.5)

*Percent (standard error) of cow inventory on January 1 of that year

Source: NAHMS Dairy Studies. Dairy 2007 Part II: Changes in the U.S. Dairy Cattle Industry, 1991-2007[5]; page 73.

Mastitis Incidence, Somatic Cell Count, and Antibiotic Usage

The NAHMS reports indicated that the percentage of U.S. dairy cows with clinical mastitis increased slightly from 1996 to 2002, and again in 2007 (Table 4)

Table 4. Percent U.S. Dairy Cows with Clinical Mastitis.

1996	2002	2007
*13.4 (0.3)	14.7 (0.3)	16.5 (0.5)

*Percent (standard error) of cow inventory on January 1 of that year

Source: NAHMS Dairy Studies. Dairy 2007 Part II: Changes in the U.S. Dairy Cattle Industry, 1991-2007[5]; page 75.

Although the slight increase in mastitis incidence from 1996 to 2002 might be associated with a more than doubling in the percentage of cows given bST (Table 3), mastitis incidence

continued a trend upwards in 2007 despite a 5% decrease in the percentage of cows given bST. A more likely relationship might be found with the increased annual yield of milk per cow each year (Table 1).

Despite the slight increases in clinical mastitis over the 3 study years for the NAHMS Dairy reports, bulk tank somatic cell count generally decreased. Bulk tank somatic cell count (BTSCC) refers to the number of white blood cells (leukocytes) and secretory cells per milliliter of raw milk and is used as a measure of milk quality and udder health. Increased BTSCCs are generally associated with increased intramammary infection and decreased milk production. The current regulatory limit for BTSCCs in the United States is 750,000 cells/ml. Although the U.S. regulatory limit is 750,000 cells/ml, producers may lose quality premiums or receive less money for their milk if it does not meet the quality guidelines determined by the processor who purchases the milk[7, 8].

The majority of U.S. dairy operations had an average BTSCC between 100,000 and 299,000 cell/ml during each of the three NAHMS study years[7]. The BTSCC from 4 of the 10 U.S. Federal Milk Marketing Orders were analyzed from 1995 to 2006 and decreased over that period[5]. This trend continued through at least 2011[8].

The 2002 and 2007 NAHMS studies surveyed the use of antibiotics to treated specific disease in U.S. dairy cattle. Treatment with antibiotics remained a key therapy for clinical mastitis. Based on these surveys, 91.9 and 89.9 percent of cows affected with mastitis were treated with antibiotics in those years, respectively[7].

Violative Drug Residues in U.S. Milk Supply

The U.S. dairy industry has clearly undergone significant changes in the past 20 years. In terms of public health, the potential for antibiotic residues in milk is a significant concern regardless of the demographics of the dairy industry. As noted in the 2002 and 2007 NAHMS Dairy reports, antibiotic usage is a predominant therapy for clinical mastitis. Because sometribove was found to increase the risk of clinical mastitis in treated dairy cows, it was appropriate at the time of its approval to consider whether this increased risk could also lead to more antibiotic residues in the U.S. milk supply.

Data from the U.S. National Drug Residue Milk Monitoring Program obtained during the first few years after sometribove commercialization provided some of the information used by the Joint FAO/WHO Expert Committee on Food Additives in 1998 to conclude that sometribove use would not increase antibiotic residues in milk. Now that sometribove has been commercially available for 19 years, it is valuable to review subsequent data from this Program to reevaluate the initial conclusions regarding the impact of bST on antibiotic residues in milk.

The U.S. Grade A Pasteurized Milk Ordinance (PMO) requires that all bulk milk tankers be sampled and analyzed for animal drug residues before the milk is processed. Any bulk milk tanker found positive is rejected for human consumption[9]. Mandatory reporting of data from this program is required by state regulatory agencies under the National Conference on Interstate Milk Shipments (NCIMS). Data are reported on the extent of the national testing activities, the analytical methods used, the kind and extent of the animal drug residues

identified, and the amount of contaminated milk that was removed from the human food supply. The system includes all milk, Grade A and non-Grade A, commonly known as manufacturing grade. Grade A milk represents approximately 95% of the milk supply in the U.S.

The National Milk Drug Residue Database (NMDRD) provides results of this voluntary industry reporting program. The FDA and the NCIMS developed the cooperative, federal-state program to ensure the sanitary quality of Grade A milk and milk products shipped in interstate commerce. The data base is operated by an independent third party under contract to the FDA. As of October 31, 1994, all fifty States and Puerto Rico were participating in the data base program.

Annual reports from the NMDRD for Fiscal Year 1994 through 2012 are available to the public via the contractor's website[10]. The reports provide test results of bulk milk tankers, for which samples are taken on receipt of every tanker load at a milk receiving facility. Milk from individual producers and pasteurized fluid milk and milk products at each processing facility are also tested periodically each year. Results for bulk milk tankers are presented in Table 5.

Table 5. National Milk Drug Residue Data Base Antibiotic Testing Results for Bulk Milk Tankers.

Fiscal Year	Period Covered	Total Samples	Number Positive	Percent Positive	Disposition (pounds)
1994	10/1/93 – 9/30/94	3,213,220	2,024	0.063%	62,768,000
1995	10/1/94 – 9/30/95	3,219,071	3,263	0.101%	105,144,000
1996	10/1/95 – 9/30/96	3,384,779	3,530	0.104%	115,952,000
1997	10/1/96 – 9/30/97	3,526,327	3,274	0.093%	108,251,000
1998	10/1/97 – 9/30/98	3,383,659	2,965	0.088%	102,265,000
1999	10/1/98 – 9/30/99	3,267,230	2,770	0.085%	98,778,000
2000	10/1/99 – 9/30/00	3,501,878	2,542	0.073%	88,890,000
2001	10/1/00 – 9/30/01	3,280,036	2,191	0.067%	79,913,000
2002	10/1/01 – 9/30/02	3,623,702	2,212	0.061%	80,043,000
2003	10/1/02 – 9/30/03	3,571,834	1,899	0.053%	70,106,000
2004	10/1/03 – 9/30/04	3,589,082	1,571	0.044%	58,280,000
2005	10/1/04 – 9/30/05	3,432,547	1,307	0.038%	49,444,000
2006	10/1/05 – 9/30/06	3,431,165	1,312	0.038%	78,406,000
2007	10/1/06 – 9/30/07	3,303,479	1,052	0.032%	83,121,000
2008	10/1/07 – 9/30/08	3,364,572	958	0.028%	40,551,000
2009	10/1/08 – 9/30/09	3,311,437	861	0.026%	35,201,000
2010	10/1/09 – 9/30/10	3,204,371	802	0.025%	33,457,000
2011	10/1/10 – 9/30/11	3,182,972	671	0.021%	26,874,000
2012	10/1/11 – 9/30/12	3,196,413	542	0.017%	23,207,000

It should first be mentioned that U.S. violative residue data reviewed by JECFA in 1998 for the period 1992-1994 revealed that the average percent of milk discarded was 0.06% in 1992 and 1993 and 0.07% in 1994 after sometribove commercialization, with a further increase in 1995 to 0.09%. Table 5 provides the percent of bulk milk tanker samples that were positive, and the trends reported from 1994 through 1996 show a similar increase. The JEFCA report noted, however, that this increase coincided with a change in the

screening procedures in most states to include more sensitive tests[3]. Nevertheless, results of the 1996-2012 surveys revealed that the percent positive tankers has declined nearly every year. Between 1996 and 2012 there has been over an 80% reduction in percent of positive samples from bulk milk tankers, with 0.017% of samples found positive in 2012.

Results from samples of pasteurized fluid milk and milk products are provided in Table 6.

Table 6. National Milk Drug Residue Data Base Antibiotic Testing Results for Pasteurized Fluid Milk and Milk Products.

Fiscal Year	Period Covered	Total Samples	Number Positive	Percent Positive	Disposition (pounds)
1994	10/1/93 – 9/30/94	61,775	3	0.005%	421,000
1995	10/1/94 – 9/30/95	70,381	8	0.011%	189,000
1996	10/1/95 – 9/30/96	78,557	2	0.003%	0
1997	10/1/96 – 9/30/97	65,379	3	0.005%	388,000
1998	10/1/97 – 9/30/98	60,905	3	0.005%	128,000
1999	10/1/98 – 9/30/99	55,478	2	0.004%	163,000
2000	10/1/99 – 9/30/00	53,761	4	0.007%	127,000
2001	10/1/00 – 9/30/01	63,996	2	0.003%	79,000
2002	10/1/01 – 9/30/02	56,596	3	0.005%	5,000
2003	10/1/02 – 9/30/03	54,932	8	0.015%	64,000
2004	10/1/03 – 9/30/04	57,875	4	0.007%	49,000
2005	10/1/04 – 9/30/05	53,106	8	0.015%	60,000
2006	10/1/05 – 9/30/06	44,956	1	0.002%	46,000
2007	10/1/06 – 9/30/07	43,851	2	0.005%	40,000
2008	10/1/07 – 9/30/08	43,940	3	0.007%	113,000
2009	10/1/08 – 9/30/09	45,601	0	0.000%	0
2010	10/1/09 – 9/30/10	44,777	1	0.002%	49,000
2011	10/1/10 – 9/30/11	48,566	0	0.000%	0
2012	10/1/11 – 9/30/12	40,882	0	0.000%	0

The surveys reveal that the percent of samples of finished milk and milk products that tested positive were very low during the entire 1994 to 2012 period, from 0 to 0.015%.

SUMMARY

The U.S. dairy industry has undergone significant changes both before and during the 19 years that sometribove has been commercially available. Dairy farm operations have decreased substantially in number, but increased in size, and average milk production per cow has steadily increased. Mastitis rates slightly increased between 1996 and 2007, and antibiotic treatment is still a treatment of choice to treat the disease. Use of bST on U.S. dairy farms increased from 1996 to 2002 and remained at moderate usage rates at the time of the 2002 and 2007 surveys, i.e., ~15% of dairy operations and ~20% of cows.

Despite tremendous changes in the industry, U.S. milk quality has consistently improved. Incentives to produce quality milk are strong. Bulk tank somatic cell scores above the legal limit and/or positive test results for antibiotics can lead to significant financial penalties, suspension of the producer's permit to sell milk, and export limitations.[7,8,9] In 2002 and 2007, over 40% of U.S. dairy operations participated in milk quality assurance programs[5].

During the years that sometribove has been available commercially, U.S. bulk tank somatic cell scores declined, and the percentage of bulk tanker trucks testing positive for antibiotics has greatly decreased. Finished milk products continue to test very low for antibiotic residues. The risk of increased mastitis rates and somatic cell counts associated with the use of sometribove appears to have been well-managed in the U.S. dairy industry since its commercial availability. Initial conclusions that there would be no increased risk of drug residues in milk due to bST commercialization appear to have been valid.

REFERENCES

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[9]Grade “A” Pasteurized Milk Ordinance, 2009 Revision.

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