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REGULATION OF RBST IN THE US

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In the United States (US) and European Union (EU) the regulatory and commercialization process for recombinant bovine somatotropin (rbST) had widely differing outcomes. Although the regulatory process in both locations was completed in 1993 the commercialization of rbST in the US has been highly successful while completely failing in the EU. This paper examines these events from the US perspective and concludes that reasons for the difference in commercial success lie in the cultural, regulatory, and political background differences between the two world locations.

Key words: somatotropin; dairy cattle; regulatory process; public acceptance.

This paper provides a US perspective on the approval and regulation of recombinant bovine somatotropin (rbST). It also provides a chronology of the key events that have taken place in the US, as well as in the EU with respect to rbST. This paper is organized as follows: the present status of rbST in the US and Europe is reviewed first. A brief historical overview of how the US and the EU reached their current positions on rbST is given next. Finally, the factors that led to the differing outcomes in the EU and the US are delineated, along with lessons that have been learned from the case of rbST. Parallels are drawn with current developments in genetically modified (GM) foods.

The Current Status Of rbST

In the US, Posilac® is the brand name of Monsanto's rbST, a two-week formulation administered by subcutaneous injection in lactating dairy cows. It is the largest selling pharmaceutical product in the history of the dairy industry. In a time span of 6 years, approximately 35 - 40 percent of US dairy herds have adopted use of Posilac®. This parallels fast adoption rates of other non-agricultural biotechnologies.

Technical approval of rbST was achieved in the EU in 1993, the same year as the US. However, in the EU there is currently a ban on rbST sales and research. This ban remains in place indefinitely, even though the human safety of rbST has been reaffirmed by both the US and EU, and milk and milk

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products from cows injected with rbST in the US are not prevented from entering the European Union, therefore, no trade barriers exist to milk products from US dairy cattle treated with rbST.

The differing EU and US regulatory approval outcomes have taken place in a constantly changing period for world agriculture. Worldwide, high yield, intensified agriculture is being scrutinized for its environmental, human health impacts as well as its effects on land use and rural human communities. Projected world population growth, and the increasing need for advances in agricultural productivity to provide safe and nutritious food for animals and humans while protecting the environment are continual issues. The public debate on the use of biotechnology, and the public's concerns of chemical-use in agriculture and its links to human health, have been dominant frames throughout the period of rbST approval and commercialization process. However, these and other similar factors have played out differently in EU and the US. The approval process was successful in both locations, it was the commercialization process that differed. This paper attempts to answer why this may be the case.

The History Of rbST

The effects of bovine somatotropin (bST) in cattle were first reported by two Russian scientists, (Azimov & Krouze, 1937). These investigators found that an active principle extracted from the pituitary glands of cows increased milk production. Their study, published in the American Journal of Dairy Science, was seminal in the field. Their major conclusions from this study indicated there were no adverse effects on cow health, a consistent increase in milk yield that was influenced by the quality of management of the farm, and that milk yield returned to previous levels after completion of treatment. These findings still hold true today. The active compound in the pituitary extracts was later identified as bST (Young, 1947). During World War II, English scientists confirmed the effects of somatotropin in goats, as well as cows, and considered it a potential way to increase food production (Cotes *et al*., 1949). However, these scientists were unable to supply enough somatotropin from slaughterhouse-derived pituitaries to make it a practical reality.

In the 1960's, Monsanto initiated a research program in bST (Machlin, 1972). Monsanto, a chemical company at that time, saw a business opportunity if a chemically synthesized fragment of the bST molecule that was active could be found. This active fragment would then be used to duplicate all the effects of bovine somatotropin. Following extensive scientific studies it was discovered that all 190 amino acids would be needed in order to simulate the desired effects of bST. At the time, a protein that large could not be chemically synthesized. So the program was terminated and all the scientists were assigned to other projects or laid off. Yet the program had left its mark on Monsanto, as it signaled a large business opportunity, if another way to produce bST could be found. Hence, the stage was set for recombinant bST or rbST.

1973 was a pivotal year for chemical companies, such as Monsanto, because this was the year of the world oil crisis. Operating profit at Monsanto dropped 88 percent as a result of oil price increases. Monsanto realized its profits were directly tied to oil and that it would need to eliminate this dependency in the future. Biotechnology was seen as an opportunity to get away from this dependency. So Monsanto invested in a number of biotechnology companies, one of which was a startup company called Genetech. Between 1973 and 1981, through a series of consultations, Genotech agreed to produce rbST for Monsanto. Genetech produced Monsanto's first bovine somatotropin, being the first animal molecule that it cloned, (Leonard-Barton & Pisano, 1993).

By 1982, efficacy trials of rbST had begun in the US. These trials set out to determine if a full lactation increase was possible, because previous studies had only used small amounts of material.

No one had yet proven that a cow could be treated through the entire lactation period and still remain healthy. At Cornell University, Professor Dale Bauman (Bauman *et al*., 1985) conducted the initial studies and demonstrated that cows remained healthy while maintaining an increase in milk production.

By 1983, Monsanto had committed to a worldwide effort to get rbST approved, and had started European trials, as well as continuing the US trials. Opposition to bST in Europe started earlier than in the US and was based on concerns about food safety and impact on small farms. The first hint that there might be a backlash in the US came following an economic study conducted by Kalter *et al*. (1985) at Cornell University. Kalter *et al*. (1985) utilized results from the first full lactation study conducted at Cornell University (Bauman *et al.,* 1985) which had reported that at the highest application dose milk production could increase by as much as 40%. Kalter *et al*. (1985) suggested that if rbST was rapidly adopted in the dairy industry, with a resultant 40% increase in milk production, about 30% of dairy farmers would go out of business within 5 years of approval. This study immediately got the attention of the dairy industry, particularly its implications for the dairy industry worldwide. Of course, the scenario of a 40% increase in milk production was just one potential outcome. In fact, the average increase is approximately 15% which is similar to the effect of switching from 2 times to 3 times daily milking, a common practice in the dairy industry (Bauman, 1992). Concerns about impacts on small farms and milk prices had the effect of uniting some farming groups with consumer activists opposed to the new technology.

Between 1985-1986 there was much anti-rbST activity, mostly on the part of consumer advocates, such as Jeremy Rifkin, who were opposed to biotechnology. The Green Movement in Europe was also active in what at that time Monsanto considered to be low-key opposition to the technology. Ironically, the first rbST plant was built in Europe because it was considered highly likely that European approval would occur first. In fact, a survey of consumers in the United Kingdom (UK) in 1985 indicated that more than 70% believed the initials BST stood for British Summer Time.

In 1987, the first submissions where made for approval in France, the UK, and in the United States. At that time, submissions were made to member countries intended as markets for the product. France and the UK were two European markets that were initially selected.

The first large investigation of the rbST approval process in the US started in 1989 when Senator Lehy of Vermont requested a General Accounting Office (GAO) investigation (GAO, 1994). The debate at this point was not only public but was also becoming political. By 1990, the EU had established a moratorium on rbST approval until the end of the year. This moratorium was imposed just in case approvals occurred, and in order to ensure that EU countries would not market the product. In the United States, the National Institutes of Health (NIH) held a public hearing and reviewed the human safety aspect of rbST, reaffirming its safety (NIH, 1991).

Public hearings similar to those conducted in the US were never held in Europe. In the US, investigations were public -- the GAO (GAO, 1994) and the Inspector General's (IG) Office (Kusserow, 1992) were involved in the review process and their findings were released as public documents. These debates exposed the issues and allowed the public to get involved. They were all open; anyone could attend hearings and seek permission to speak. A large number of groups did. In Europe, however, there was almost no public discussion.

The Office of Technology Assessment (OTA) in the US issued a report in 1992 (OTA, 1992), the same year as the EU extended its' moratorium on rbST. This report, along with a report from the US Inspector General's Office, found that the processes by which safety data was collected, or how the Food and Drug Administration (FDA) provided oversight of the technology were appropriate.

Monsanto received its final favorable opinion from the Committee of New Medical Products (CVMP) in 1993. At about the same time, the FDA held a public hearing on concerns expressed about mastitis being caused by the use of rbST in cattle. The Veterinary Medical Advisory Committee (VMAC) chaired a public hearing on the mastitis issue alone, which was also published (Collier, 1993). In 1993, there was also a ninety-day moratorium placed on rBST sales that was enacted by congress and allowed the FDA to develop a Post-Approval Monitoring Program (PAMP) to evaluate impact of rbST use in the dairy industry on cattle health and milk quality. These results were presented in two public hearings after 6 and 12 months of commercial sales.

Late in 1993, the FDA approval process was completed in the United States. In the EU, the moratorium placed on rbST was extended with almost no public debate. The only debate carried out in Europe was in the press. Meanwhile, in the United States sales began in 1994 with the FDA issuing guidelines for voluntary labeling. At the same time that sales began, the PAMP was initiated to reassure consumers that Posilac® labels were accurate that there were no changes in the safety of the milk supply. The occurrence of antibiotics in milk was monitored for 50 percent of the US milk supply.

Monsanto markets Posilac® directly to producers so that every time a producer ordered the product, they could be queried on any concerns they may have regarding product safety. Farmers indicating any concerns about treated cows automatically became adverse experiences and were reported to the FDA. This was probably the most extensive PAMP ever carried out on an animal drug, and the results of this program were publicly reported. There were two post-approval periods -- 6 months and one year post-approval. In addition, the FDA issued reports every 6 months on adverse experience indications and any other concerns that might have arisen. Hence, there was in-depth oversight and monitoring during the early introduction of rbST. In 1994, the EU extended the moratorium for a further 5 years. In 1999, the FDA reaffirmed the safety of rbST for humans in direct response to a letter from some members of congress. In 1999, Canada rejected the somatotropin license that Monsanto had submitted. This rejection was based on cow health concerns. In 1999, the EU extended the moratorium to an outright ban.

How US Consumer Concerns Were Addressed

The fundamental concerns of US consumers were not substantially different from those in other regions of the world. United States consumers were concerned about the impact of rbST on small farms, human food safety, and animal welfare. Much work was done in response to these concerns. There have been several independent studies carried out which examine the impact of rbST on small farms, specifically in regard to the impact on herd size, the longevity of cows in the herd, as well as, the kinds of problems experienced in implementing the technology (Bauman *et al*., 1999; Judge *et al.*, 1997; Ruegg *et al.*, 1998; Van Amburgh *et al*., 1997; Tauer & Knoblauck, 1997). Probably the most notable of these studies was one conducted on herds located in the Northeastern United States (Bauman *et al*., 1999). These were small dairies in the Northeast -- herds were not greater than 250 dairy cows in most cases. This study compared the lactation records of farms that adopted rbST five years post-approval and treated at least fifty-percent of the herd to those that never adopted use of rbST during the same time period. The study demonstrated that in herds adopting use of rbST, the herd size increased; adopting farms were also able to invest more; there was no change in longevity of cows in the herd; there was no difference in the reproductive performance of the herd, and there was no difference in mastitis incidence. In another study, (Tauer & Knoblauch, 1997) increased profits from the use of Posilac® were reinvested in the farm but no size bias was shown.

The human food safety impact of rbST was also studied closely. Each evaluation has been carried out in a public forum. The FDA has repeatedly provided opportunities for the public to openly participate in evaluating the human safety component of rbST. Information provided by studies on human health demonstrated safety (Juskevich & Guyer, 1990; Hammond *et al.*, 1990). Third parties were very important to the debate. For instance, the American Cancer Society negated concerns that rbST could potentially be carcinogenic. Then the animal welfare component was essentially evaluated in the PAMP, and again there were two public hearings that allowed open participation. These meetings were heavily covered in the farm press.

The Safety Of rbST

When a cow is treated with rbST the concentration of bST in milk does not change. This is one of the reasons why a cow cannot be detected that has been treated with rbST. The concentration of rbST in milk is extremely low-- about one part per billion. When milk is pasteurized, and there is only one dairy in the US that does not pasteurize milk, the rbST is destroyed. This is independent of the fact of that the concentration of bST in milk does not change when you treat a dairy cow with rbST. When milk is consumed the somatotropin is broken down like every other protein. There are hundreds of proteins in milk, of which somatotropin is an extremely small component. Casein is the primary milk protein that makes up 85% of the protein in milk and this is considered a "foreign protein." The term "foreign protein" has been used in the public arena to increase the perceived risk of the technology on the part of the public. Foreign proteins, however, are a normal part of foods that humans consume.

Concerns voiced about rbST include the fact that its concentration would increase in milk, that it can escape destruction of pasteurization and digestion, and that it will have a biological effect – usually something like cancer. Based on existing knowledge, as explained above, the probability of such a series of events occurring is not measurable. To this even it should also be added that studies have shown (Juskevich & Guyer, 1990) that if a person is injected with somatotropin there are no detectable effects. It does not bind to the human growth hormone receptor (Hammond *et al.*, 1990).

Another safety concern has been made that cows treated with rbST will experience more mastitis, causing dairy farmers to use more antibiotics, which, in turn contaminate milk and cause allergic reactions in people. It is a proven fact that with an increase in milk production there is an increase in mastitis. This is part of the body of evidence that has accumulated under the mastitis review process (White *et al*., 1994). The use of antibiotics is an individual management decision on the part of the dairy farmer. Some farmers use antibiotics intensively while others do not -- usage can vary quite dramatically. But even if a dairy farmer did use antibiotics more intensively a series of events would have to occur in order for those antibiotics to end up in the milk supply. At each point in the supply chain -- from the dairy farmer to the consumer -- the milk is sampled and tested. Hence, the truck driver who collects the bulk tank of milk takes a sample from every milk tank that they collect at the farm. Every truck that delivers to the processing plant is then sampled. When the milk goes into the silo it is sampled every day. If any sample is found to contain antibiotics it is disregarded. It is therefore extremely unlikely that a contaminated sample would be delivered to retail stores for human consumption. It is very difficult to get an antibiotic concentration in milk high enough to cause a serious problem within the human population.

Labeling Of rbST

The United States has made significant progress on labeling. Labeling has to be truthful and it has to be informative. The basis for mandatory labeling is a change in the characteristics of the food being sold, for example, if an ingredient is added, or if the concentration of some ingredient is changed. Labeling a food product based on production practices may be done on a voluntary basis appealing to

interested consumers while still making valid claims. In the case of rbST, the biotechnology industry supported voluntary labeling other voluntary labels include organic milk and cheese, which allows for the use of recombinant rennet (chymase) produced through biotechnology.

Lessons Learned From rbST

There are several lessons that can be learned from the acceptance of rbST in the United States and its rejection in the European Union.

Factors in US Acceptance of rbST

- One of the key factors that facilitated the commercialization and acceptance of rbST in the US was that the political process did not interfere with the ability of Monsanto to continue conducting its research and studies. If a firm or university can not provide data for regulators to evaluate, there is no way to satisfy questions about safety. Because Europe did not allow Monsanto, or any other university or firm for that matter, to conduct safety studies, it greatly reduced the chance of rbST being approved.

- Another important factor was the elimination of dairy subsidies in 1985. The case could no longer be made that Monsanto was being subsidized through increases in milk production paid by taxpayers. The price support in place was so low that it was never triggered in the post approval period.

- Similarly, the congressional hearings were highly publicized in the US, which allowed not only attendance by members of the national press but also the farm press. The hearings were well covered and highly commented on so that the public as a whole was kept aware of recent developments.

- Third parties also participated in the public debate. These parties were considered to be independent and reliable sources of information by the public. Independent sources included the American Pediatric Society, the American Cancer Society, the Dietetic Association, and so on. All of these groups were able to provide direct, reliable sources of information to consumers.

- Finally, the PAMP that was carried out in the US was very successful. Similarly, the voluntary labeling program allowed milk to be labeled from cows not treated with bovine somatotropin, as long as there were no health claims made that the milk was any different. Voluntary labeling allowed people seeking non-rbST milk to find it.

Factors in European Rejection of rbST

The EU situation, however, was different from that in the US.

- Bovine spongiform encephalopathy (BSE) or "mad cow" disease set the stage for a low level of confidence in the EU regulatory process. The formation of the European Union changed how the whole food regulatory process was structured. This led to an unfavorable climate towards acceptance.

- A parallel ban on steroid (non-peptide) growth hormones created yet another negative influence on public attitudes.

- The Green Movement came out strongly against biotechnology. This stance ultimately contributed to the negative climate of public opinion in Europe.

- The European press became very polarized about biotechnology. It did not report two sides to the story, and before very long the public was polarized as well.

- The policy environment was equally unsuitable. The EU's common agricultural policy (or CAP), directly subsidizes milk output. An increase in milk production from the use of rbST would therefore lead to a perceived increased cost of the subsidies. This effect was unpalatable both from the government's and from the public's perspective. In all, there was little support for somatotropin in Europe.

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