Dairy Products Used To Make Pharmaceuticals And Related Compounds

Immunized dairy cows are producing antibodies that can be used to treat gastrointestinal tract infections. Transgenic goats and cattle are being developed to produce proteins—such as antithrombin III, human-serum albumin, alpha-1 proteinase inhibitor, and human lactoferrin—used in the treatment of infections and diseases. Dairy products also are used to produce low-cost, optically pure chiral intermediates for the pharmaceutical, food, and agricultural chemical industries.

The dairy industry is expanding beyond traditional items, such as milk, cheese, butter, and ice cream, to include the production of pharmaceuticals and related high-value chemicals. Technology is now available that allows the production of antibodies and other compounds in the milk from dairy cows and other farm animals. Using animals, companies can produce significant quantities of high-value proteins at relatively low cost. These compounds are then used by the food, pharmaceutical, and chemical industries in various applications.

Significant research has been conducted by both public and private entities on using various types of animals to produce special chemicals. The following information describes products and activities under development by a few private firms.

Immunized Dairy Cows Are One Source

GalaGen Inc., a pharmaceutical company located in Arden Hills, Minnesota, immunizes pregnant cows using proprietary immunization agents and regimens. After calving, the antibody-rich colostrum is collected from the first several milkings and processed using highly refined techniques that concentrate and preserve the antibodies. The antibodies, or immunoglobulins, have the potential for both treating and preventing infections, primarily in the gastrointestinal tract. They are taken orally, either in a solid-dosage form or as a liquid reconstituted from a dry powder. Initial disease targets for GalaGen products include:

- Yeast infections of the mouth and esophagus caused by *Candida albicans*,
- Ulcers and gastritis caused by *Helicobacter pylori*,
- Antibiotic-associated diarrhea caused by *Clostridium difficile*, and
- AIDS diarrhea, caused by *Crypotosporidium parvum*.

Since the antibody products are derived from milk, they are likely to be tolerated by humans with minimal side effects. GalaGen's strategy is to first demonstrate the safety and efficacy of these products as therapeutic agents, and later to exploit the technology's value for disease prevention.

Due to the speed with which GalaGen can develop products, the relatively low cost of manufacturing, and the anticipated safety of the products, new therapeutic antibody products can be developed at a fraction of the cost of traditionally derived pharmaceuticals. GalaGen estimates that antibodies produced from dairy cows may cost as low as $1 per gram, while a similar product from cell-culture systems might cost $10,000 per gram. Also, the investment costs for cell culture could be as high as $300,000, while costs associated with a single dairy cow would be no more than a few hundred dollars annually.

GalaGen produces its antibodies through a highly efficient system that links local veterinarians, dairy farmers, and the Land O'Lakes (LOL) procurement system. LOL is a dairy marketing and input supply cooperative with 300,000 members in 15 States. LOL's procurement system meets rigorous USDA and U.S. Food and Drug Administration standards for milk quality and sanitation. Cows calve annually and produce over a pound of antibody in the first several milkings after the calf is born. With over 5,000 dairy farms in the LOL system, more than 150 tons of antibody product could be available each year.

Transgenic Animals Another Possibility

While GalaGen and other companies develop products through an immunization route, other firms are developing innovative products by developing transgenic animals. These animals are developed by physically inserting a new segment of DNA into the genes of all cells, including the reproductive cells, so that the new DNA is transmitted to offspring as a continuing trait. This is typically accomplished using test tube technologies where the DNA is micro injected into early-stage fertilized embryos. Transgenic animals were first developed in 1980-81.

Genzyme Transgenics, located in Framingham, Massachusetts, has successfully developed transgenic technology in mice and goats. Several proteins have been successfully developed and are in various stages of development, testing, and commercialization. Genzyme's Antithrombin III (AT-III), monoclonal antibodies, and other human-protein products represent a potential revenue of $300 to $400 million, according to a prospectus developed by Payne Webber in 1994.

AT-III is a blood-clotting protein usually present in human blood. Individuals lacking normal production of AT-III suffer from a high incidence of inappropriate blood clotting, especially in the lungs and extremities. It is estimated that AT-III deficiency is inherited by one in every 5,000 to 10,000 individuals. Acquired AT-III deficiency can result from illnesses—including certain liver diseases, acute venous thrombosis, septicemia (blood poisoning), and disseminated intravascular coagulation—surgical procedures, and the use of oral contraceptives.

Genzyme Transgenics established a joint venture with Sumitomo Metals in September 1990 to develop recombinant AT-III in transgenic animals. They have achieved expression levels of AT-III in the milk of transgenic mice at concentrations of more than 10 grams per liter. Transgenic goats also have been developed, with expression levels of up to 7 grams per liter in the milk. The company has produced several transgenic goats with the AT-III gene, and selected a founder goat from which their production herd is being generated. This goat has approximately 4 grams of AT-III per liter in her milk. Genzyme Transgenics expects to begin clinical studies in 1996. The company projects the worldwide market to be in excess of $300 million annually. Currently, AT-III is derived from human plasma. Payne Webber estimates that the demand for AT-III could be satisfied by about 300 transgenic goats, which would be much more economical than providing the product from increasingly expensive human plasma.

Another product developed by Genzyme Transgenics is human-serum albumin (HSA), which is a major protein component of human plasma. It is used clinically as a blood-volume expander and to increase the levels of blood protein in trauma, shock, and post-operative recovery. HSA has been expressed in transgenic mice at a level of 10 milligrams per liter of milk. The company is working on transferring HSA genes into goats in 1995.

Alpha-1 proteinase inhibitor, which is used to treat inherited alpha-1 antitrypsin deficiency, is being developed for possible use against atopic dermatitis, a chronic inflammatory skin disorder with symptoms of severe itching that is common in young children and maybe inherited. This disease affects close to 2 million Americans. Preliminary studies have shown significant clinical improvement of patients after treatment with alpha-1 proteinase inhibitor. A pilot study was initiated in March 1995 at the Boston University School of Medicine and Mount Sinai Hospital to confirm the preliminary results. Alpha-1 proteinase inhibitor has been expressed in high levels in mice and rabbits, and work has begun to develop this protein in goats.

Another company, GenPharm Europe (now GenPharm International headquartered in Mountain View, California) developed the world's first transgenic bull. Born in December 1990, GenPharm's Herman was genetically engineered to bear human genes and pass them on to his offspring. In 1994, the breeding program produced 55 bovine pregnancies, of which half were transgenic. The animals carry a gene for producing human lactoferrin (HLF) in cow's milk. Lactoferrin, an orally active protein produced naturally in human milk, has antibacterial, iron transport, and other important properties.

GenPharm plans to build a herd of several hundred transgenic cows to produce HLF on a large scale. Milk from each cow should contain several grams of HLF per liter. With each cow expected to produce up to 10,000 liters of milk per year, this would result in thousands of kilograms of HLF annually. The milk will be processed by removing water and milk fat, thus yielding milk powder containing HLF for use as an ingredient in oral formulations. The company eventually hopes to subcontract milk production to farmers or dairy cooperatives, similar to the strategy being used by GalaGen.

GenPharm intends to market HLF to populations that are at risk for bacterial infections of the gastrointestinal tract. This includes cancer patients whose immunity is lowered by chemotherapy, AIDS patients, and premature infants. Like GalaGen, GenPharm expects regulatory approval to be easier with milk products than with other genetically engineered products. The company also believes that transgenic dairy cattle are the only viable commercial route to making sufficient volumes of HLF to serve such a large market.

Chiral Compounds Made From Whey

Another company, Synthon Corporation, uses proprietary synthesis technologies to produce low-cost, optically pure chiral intermediates for the pharmaceutical, food, and agricultural chemical industries. Chiral compounds have the same chemical composition, but they have different physical geometries—they are mirror images of each other. This has implications for pharmaceutical and other industries since each form, or enantiomer, of the same drug can affect biological systems in different ways. Synthon's first product is a chiral lactone, optically pure (S)-3-hydroxy-gamma-butyrolactone, known as HGB, which is used by the pharmaceutical industry as a protein inhibitor for AIDS and a vitamin source.

Synthon has exclusive license to technologies developed at Michigan Biotechnology Institute and Michigan State University. The company uses whey and other inexpensive feedstocks, such as corn and wheat starch, to produce the chiral compounds. Synthon's production process uses water as the reaction's only solvent and processing temperatures of less than 70°C, which is safer than many conventional methods that produce chiral intermediates with toxic substances. The company has already shown that the process can be easily scaled up. They can produce 100 percent optically and chemically pure HGB, which can be sold for under $500 per kilogram. Current prices range from $1,000 to $4,000 per kilogram for a less pure product.

The 1993 worldwide market for chiral drugs was estimated at $9.2 billion for bulk active compounds and $32.4 billion for final dosage form. That represents a 16-percent increase in both categories from 1992. The worldwide market is estimated to reach $60 billion by 1997. [Donald Van Dyne, (314) 882-0141]