

Treating Mastitis Without a Loss of Milk Revenue

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Mastitis: The Problem

Mastitis in the lactating dairy cow is considered the costliest disease to animal agriculture in the US and major dairy producing regions of the world. Annual losses are presently estimated to be upwards of \$2 Billion in the US alone. These losses are comprised of losses in milk production, discarded milk, cost of replacement animals, labor, costs of drug treatment and veterinarian costs. Mastitis refers to an inflammation of the udder, most commonly caused by a bacterial infection of the gland itself. This disease manifests itself in one of two forms: 'clinical' or 'subclinical' mastitis. Clinical mastitis has overt symptoms: the udder warm or hard, milk visibly abnormal, with clots and/or flakes. This form of mastitis usually requires intervention since the abnormal milk cannot be sold and the animal could have complications if left untreated. This is the major mastitis market for antibiotic treatments, which is at least a \$40 Million market in the US. Subclinical mastitis is associated with its own significant economic losses and is recognized as a significant contributor to clinical mastitis cases. Subclinical mastitis is considered the 'silent mastitis' or the 'silent thief' stealing profits by reducing productivity, leading to the spread of infection and increased physical and reproductive problems in the cow; its prevalence is 15-40 times higher than clinical mastitis. While subclinical disease is caused by the same bacteria that cause clinical disease, it is more difficult to recognize in the individual, since no clinical signs are visible. While there are several means currently employed in the industry to identify individuals with subclinical mastitis (e.g. milk culturing and measurement of milk somatic cell counts), the main impediment to combating subclinical mastitis is the requirement to discard milk after treatment of the infected udder until the level of antibiotic residues in the milk falls to levels deemed safe for human consumption. All currently approved intramammary antibiotics have such a discard requirement, which can range from 36 to 96 hours after treatment. Since milk from subclinically infected individuals can be sold (no visible abnormalities), treating subclinical mastitis creates an economic dilemma for the producer; long-term economic benefits of curing subclinical disease are outweighed by the short-term cost of discarded milk. Clearly what is needed is a compound that is as effective as traditional antibiotics but safe enough to be used without the milk discard requirement.

Bacteriocins

Bacteriocins are protein products of bacteria that are toxic to related bacteria. They are one of several families of molecules that arose during the evolution of Microbial Defense Systems, a form of competitive exclusion, whereby populations of bacteria must successfully compete with other organisms that coexist with overlapping nutritional and environmental niches. To do so, they

produce a vast array of compounds that are toxic to competitors, from simple organic molecules such as lactic acid, to more complex molecules such as classic antibiotics, enzymes, and bacteriocins. Within the bacteriocin family alone, there are literally hundreds of distinctive molecules; most are relatively narrow in spectrum, and active principally within-genus or within-species. Bacteriocins were discovered around the same time as traditional antibiotics (1920s) but were not developed as actively as medicines due to the narrow spectrum of activity of the bacteriocins.

One of the best studied bacteriocins is Nisin A, a 34 amino acid peptide with distinctive structures called lanthionine rings, produced by *Lactococcus lactis* (milk inhabitant), that has demonstrated activity against a number of gram positive bacteria, among which are bacteria that have evolved to survive and grow in milk. Nisin was employed in the 1940s as a food preservative because it was known to inhibit the growth of both spoilage organisms and important food-borne pathogens such as *Clostridium* and *Listeria*. Since that time, Nisin has become the most widely used bacteriocin in food preservation, being approved in over 40 countries world-wide for preservation of a wide variety of foods from cheeses to liquid eggs. With such a track record of use in food, Nisin has received GRAS (Generally Regarded As Safe) status in the US and several countries, recognizing its safety in the human food chain.

Mast Out[®]: pharmaceutical-grade Nisin A formulated for intramammary use.

ImmuCell recognized the potential of Nisin to combat mastitis pathogens (streptococci, staphylococci, and others), and acquired a portfolio of Nisin technology in 2000 for the purpose of developing an intramammary infusion product to treat mastitis. Realizing that the food-grade Nisin preparation would not be of suitable purity to become an injectable product, ImmuCell's initial focus was to develop a manufacturing process for pharmaceutical-grade Nisin A. ImmuCell filed and received a US patent on the manufacturing method it developed. Formulation of this material into an intramammary dosage form allowed pilot evaluations in mastitic cows. The result of these studies led to full-blown drug development of Mast Out[®] as a treatment for subclinical mastitis, with the goal of US Food and Drug Administration (FDA) approval of this product with two important product features:

- 1) Achieve efficacy that is equal to, or better than, traditional antibiotics against subclinical mastitis.
- 2) Achieve zero milk discard and zero meat withhold; a **FIRST** for any intramammary.

It is believed that these features would lead to significantly increased treatment of subclinical mastitis, essentially creating the subclinical treatment market.

Scientific/Regulatory Status of Mast Out[®]

Milk discard and meat withhold requirements for drugs intended for food animals is determined by the FDA after review of submissions by the drug sponsor to the Human Food Safety Technical Section of the New Animal Drug Application. This Technical Section is comprised of several subsections designed to evaluate the overall safety of the compound in humans who consume milk and meat from treated animals, distribution of the drug in the food animal to be consumed, potential for development of antibiotic resistance to the new drug or related drugs, and actual levels of drug in the tissues of treated animals. Mast Out[®] has been granted a **zero milk discard** and a **zero meat withhold** by the FDA after review of this body of data.

Effectiveness is generally determined by conducting a 'double blind, placebo controlled' 'pivotal field study' using product that has been manufactured using the same process that will be used commercially, in commercial dairy herds with natural disease at several geographical locations around the country. This type of study is typically conducted after several smaller 'pilot studies' have helped delineate the disease indications that would be sought after in the pivotal study. Mast Out[®] has been tested in 5 major trials, including 2 laboratory-based challenge-treatment trials in cows, 2 non-pivotal field trials, and a single, pivotal study of 295 cows with subclinical mastitis. These studies provided very consistent outcomes showing that Mast Out[®] was statistically highly significant ($p < 0.0001$) compared to placebo in the treatment of subclinical mastitis, with anticipated claims to include the following common mastitis pathogens: *Streptococcus agalactiae*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, Coagulase-negative *Staphylococcus* and *Enterococcus faecium*. In addition to the species claims, Mast Out[®] treatment led to statistically highly significant ($p = 0.003$) reductions in milk Somatic Cell Counts (marker of both mastitis and milk quality). This Effectiveness Technical Section is still under review with the FDA.

Target Animal Safety studies have been completed and show Mast Out[®] to be well tolerated and associated with no udder irritation or systemic problems. This Target Animal Safety Technical Section is still under review with the FDA.

The outstanding Technical Section that defines the critical path to FDA approval is the Chemistry, Manufacturing and Controls section that describes the manufacturing process and all the manufacturing sites. In addition, approval of this section requires the submission of documentation from three 'full scale' manufacturing batches. ImmuCell has contracts with FDA approved manufacturers of the active ingredient, syringes, and sterile intramammary product in place; however, full scale manufacturing batches are presently on hold while ImmuCell seeks a funding partner for this final aspect of the product development.

Value: Treating subclinical mastitis with Mast Out®

We believe that the unique product feature of zero milk discard will more than offset the cost to the producer of using this product in subclinical mastitis treatment, creating a strong return on investment. The product marketing message will focus on the important economic benefits resulting from effective management of subclinical mastitis.

The zero milk discard feature alone provides a milk savings of \$21 – \$81 per head from milk that would have been discarded by producers who are currently treating subclinical mastitis with antibiotics. The larger market opportunity, however, would be producers who are not treating for subclinical mastitis because there are no products currently available on the market that offer the zero milk discard feature.

Newly infected cows can be selected easily through standard dairy record systems. For example, a treatment candidate group of 1.5% - 4% of the herd each month could be selected on a typical farm. The profit return from using Mast Out® is derived primarily from four areas: increased milk production, reduced incidence of clinical flare-ups from the reservoir of subclinical disease, increased milk quality premiums related to lower somatic cell counts (SCC) and reduced culling. It's well documented that cows infected with subclinical mastitis are also limited in their milk production. Further, it has been reported that 22% of subclinical cases will require clinical treatment. It is generally accepted that the cost to treat clinical mastitis at the farm level is approximately \$175 per case. Data from our pivotal effectiveness study suggests Mast Out® will reduce the somatic cell count significantly for these treatment candidates. Increases in premium payments based on this reduction in SCC depend on the premium matrix by which the milk is being sold. These matrices vary by processor and region. Typically milk being sold for cheese production commands a much higher premium payment, for reduced SCC, than fluid milk. In general these premiums can range from a deduction of \$0.20/cwt for milk with too high a SCC to a premium of \$0.80/cwt for low SCC milk.

Mast Out® reverses the economic dilemma producers currently find themselves in regarding subclinical mastitis. It creates the ability to realize the long-term economic benefits of curing subclinical disease without the short-term cost of discarded milk. Treating subclinical disease, rather than ignoring it, could prove to have a significant economic return for herds that implement a Mast Out® program.

Forward-Looking Statement Disclaimer

This White Paper contains certain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Factors that could cause the Company's future results to differ materially from those

described in the forward-looking statements, together with other risk factors, are detailed from time to time in filings we make with the Securities and Exchange Commission, including our Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q. Forward-looking statements are based on our current information and expectations. Actual results may differ materially due to various factors, including those risks. The subject matter of this White Paper was presented at the World Animal Health Congress in Kansas City, MO. on December 8, 2011, and the White Paper was printed in the associated Conference Documentation Book. A related press release was issued by the Company on December 8, 2011.

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