An Ag-Biotech Success Story: the Bioniche *E. coli* O157:H7 Cattle Vaccine

August, 2008

Safe Harbour Statement

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Our Business Model

- Cash flow from globally marketed products in animal health.
- Establishment of proprietary food safety vaccine technologies.
- Development of proprietary and large market human cancer therapies.
- Today: Annual revenues of over $27 million (Animal Health)
- Future growth drivers:

  - MCC Suspension (*Urocidin*™) for bladder cancer in first Phase III trial
    2 registration studies (both Fast Track; SPA on 2nd)

  - A vaccine to reduce *E. coli* O157:H7 in cattle
    CFIA permit; USDA path to conditional license, first sales

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Corporate Structure

Bioniche Life Sciences Inc.

Animal Health	Food Safety	Human Health
Bioniche Animal Health	Bioniche Food Safety	Bioniche Therapeutics
• Largest Canadian-owned animal health company • Foci: ➢ Reducing reliance on antibiotics (immunology); ➢ Enhancing reproductive performance; ➢ Preventing illness (vaccines) **current sales: $27M+**	• Development of animal vaccines to help enhance food & water safety • *E. coli* O157:H7 cattle vaccine conditionally licensed • Other animal vaccines in pipeline (*Salmonella, Campylobacter, Listeria)*	• Drug discovery & development • Products based on proprietary technologies • Development: bladder cancer, peritoneal cancers (ovarian, colorectal)

Future Growth in Animal Health

Immunotherapies and **vaccines** are expected to be an area of growth: Consumers have increasing concerns about food ingredients and the negative health effects of antibiotic and chemical residues. Consequently, governments now seek to more tightly control the use of such products. This plays to a core strength of Bioniche – Prevention and treatment by immune modulation.

Bioniche expects continuing modest growth in its base business, enhanced by new geographic registrations. Future products will be derived from current development work around the veterinary applications of its MCC immune stimulants and from novel (prophylactic) animal health vaccines.

Fiscal 2009 revenues are expected to grow to $30 million – close to 10% growth from Fiscal 2008 results.

Animal to Human Health

- Early research focused on the role that certain mycobacterial preparations had on the immune system.

- A soil-borne, non-disease causing mycobacterium – *Mycobacterium phlei* – was found; became the source organism for ongoing research in immune stimulation.

- A formulation of cell walls of *Mycobacterium phlei* was developed - Mycobacterial Cell Wall Extract (MCWE); stimulated immune response in animal models and demonstrated profound anti-tumour activity. The first product developed from this formulation was *Regressin*, a cancer treatment for dogs.

- Further research showed that the immune stimulant activity of the cell walls was effective in combating bacteria and viruses. Two new products were developed and licensed – *Equimune*, for the treatment of respiratory diseases in horses and *Immunoboost*, for the treatment of bacterial diarrhea in calves.

- A Kingston, Ontario urologist, Dr. Alvaro Morales, came across *Regressin* (MCWE). Dr. Morales had pioneered the use of another mycobacterial product – BCG – to treat human bladder cancer, and wanted to explore whether MCWE might also work in this indication.

- With the leadership of Dr. Morales and a significant investment by Bioniche, an advanced formulation (Mycobacterial Cell Wall-DNA Complex - MCC) is now undergoing Phase III clinical testing in humans.

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Bioniche Food Safety

- Strategy: vaccinate animals against pathogens they may introduce to the human food and water supply, and environment.

In Development / Marketed							
Product	**Category**	**Research**	**Pre-Clinical**	**Clinical**	**Marketed**		
E. coli O157:H7	Vaccine						
Salmonella	Vaccine						
Campylobacter	Vaccine						
Listeria	Vaccine						

- First initiative: cattle vaccine to reduce colonization and shed of *E. coli* O157:H7 bacteria (North American registrations in progress)

- *E. coli* O157:H7 causes ≈**73,000 cases of infection and ≈60 deaths per year** in the U.S. *(CDC)* and a further **26,000 cases of infection per year** in Canada

About *E. coli* O157:H7

- One of hundreds of strains of the bacterium *Escherichia coli*
- Most strains are harmless; live in intestines of healthy humans and animals
- O157:H7 produces powerful toxin (Shiga/Vero toxin) and can cause severe illness
- O157:H7 appears to be a mutant that was first seen in South America ~20 years ago and has drifted north and internationally
- This strain first recognized as a cause of illness in 1982 during an outbreak of severe bloody diarrhea (traced to contaminated hamburgers in the U.S.)
- Until recently, most infections have come from eating undercooked ground beef (beef industry has spent hundreds of millions of dollars to improve production safety by implementing post-slaughter procedures; FDA has implemented holding and testing of meat products prior to shipping)

(Centers for Disease Control - CDC)

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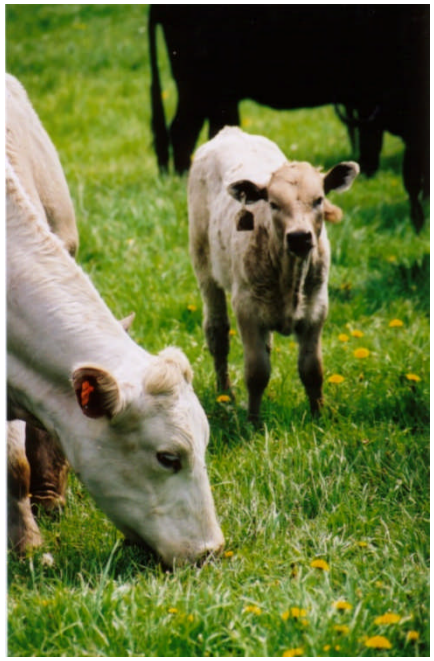
From Cattle to Humans

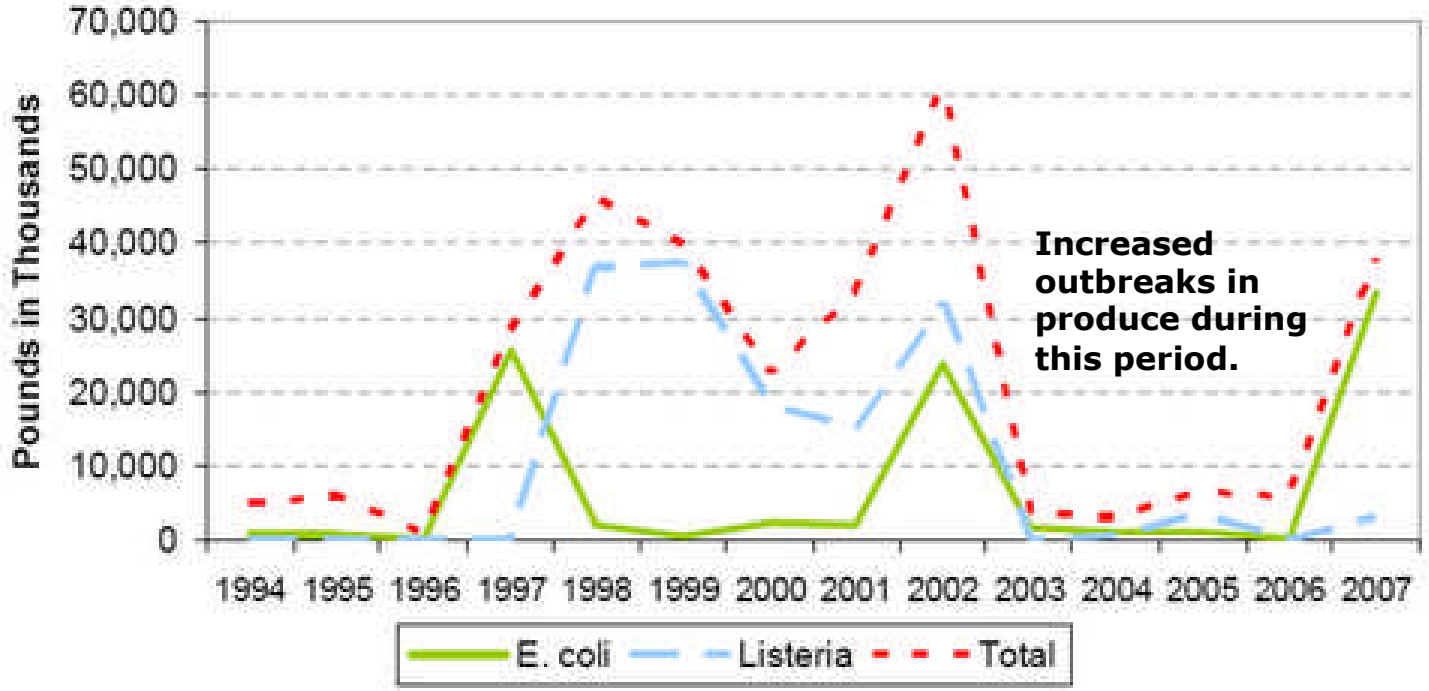


E. coli O157:H7 bacteria survives in manure, water troughs, surface water, run-off, and feed bunks; also spread by flies/birds, in dust, on hides

This bacteria is endemic in North American feedlots, affecting meat when processed. It is a global issue.

Bacteria can enter water supplies, affecting irrigation water; wells; etc.

Meat Recalls on the Rise



CRS Report for Congress
January 7, 2008
http://assets.opencrs.com/rpts/RL34313_20080107.pdf

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Effects of *E. coli* O157:H7 Infection

- Often results in severe bloody diarrhea and abdominal cramps; sometimes the infection causes non-bloody diarrhea or no symptoms.
- Usually little or no fever is present, and the illness resolves in 5 to 10 days.
- In some people, particularly children under 5 years of age and the elderly, the infection can also cause a complication called hemolytic uremic syndrome (HUS), in which the red blood cells are destroyed and the kidneys fail.
- The World Health Organization estimates that up to **10% of patients** with *E. coli* O157:H7 infection **may develop HUS**, with a case-fatality rate ranging from 3% to 5%.
- Overall, HUS is the most common cause of acute renal failure in young children. It can cause neurological complications (such as seizure, stroke and coma) in 25% of HUS patients and chronic renal sequelae, usually mild, in around 50% of survivors.

(Centers for Disease Control – CDC; World Health Organization - WHO)

Selected Outbreaks/Recalls

Sept 7 2006: **Marion Graff**, 77, of Manitowoc, Wis., dies.

Jan 26 2007: **Betty Howard**, 83, of Richland, Wash., dies.

Sept 20 2006: **Kyle Allgood**, 2, of Chubbuck, Idaho, dies.

images from USA Today

- September, 2007; 8 U.S. states
  - Topps Meat Co.; 40 people affected (2 with HUS); 21.7M lbs. recalled; Co. folded
- September, 2007; North America
  - Dole Fresh Vegetables voluntary recall of packaged salads
- June, 2007; St. Catharines, Ontario, Canada
  - 4 children hospitalized; linked to food consumption at a local restaurant
- November, 2006; 3 U.S. states
  - 99 people affected (43 confirmed); 9 hospitalized; 1 with HUS
  - Linked to consumption of lettuce at Taco Bell and other restaurants
- September, 2006; 26 U.S. states
  - 205 people affected; 3 deaths; 31 with HUS
  - Linked to consumption of fresh spinach

Common denominator in all outbreaks: cattle

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Why Vaccinate Cattle?

Brett Finlay, PhD, Professor in the Michael Smith Laboratories, and the Departments of Biochemistry and Molecular Biology, and Microbiology and Immunology at the University of British Columbia (Canada)

- Was conducting basic research in the laboratory in 1995 and made two fundamental discoveries:
  1. The *E. coli* O157:H7 bacteria secrete attachment proteins;
  2. When injected directly into a cell wall, one of these proteins serves as a receptor, to which the bacteria adhere, allowing them to colonize the intestine.
- Realized that it might be possible to immunize against the attachment proteins of the bacteria (initially thought useful in childhood vaccines; then realized that a cattle vaccine might be the better opportunity to pursue)

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Development of the Vaccine

- Dr. Finlay contacted Dr. Andy Potter at the Vaccine & Infectious Diseases Organization (VIDO - University of Saskatchewan, Canada) and suggested they try and make secreted proteins to immunize cows.

- The pair demonstrated in a pilot study that the vaccine appeared to reduce shedding of *E. coli* O157:H7 in cattle manure.

- VIDO and Dr. Finlay approached the Alberta Research Council (ARC), who later approached Bioniche. Bioniche has become the global commercial partner responsible for the technology transfer, development, scale-up, and commercial manufacture of the vaccine.

Efficacy of the Vaccine

Vaccine was efficacious in Phase II and Phase III studies involving more than 30,000 cattle:

- Reduced shedding of organism in feces
  - Reduced duration: 63.9% efficacy
  - Reduced magnitude: 2.28 $\log_{10}$ reduction
- Reduced colonization (mucosal scrapings): 98.3% efficacy
- Reduced hide contamination: 53.8% efficacy
- Reduced pen prevalence(ROPES): OR=0.59 (p=0.004)

- Vaccine efficacy improved with the number of doses administered (dose-effect)[1]

- Vaccinating a majority of cattle within a pen offered a significant protective effect ("herd immunity") to non-vaccinated cattle within the same pen[1]

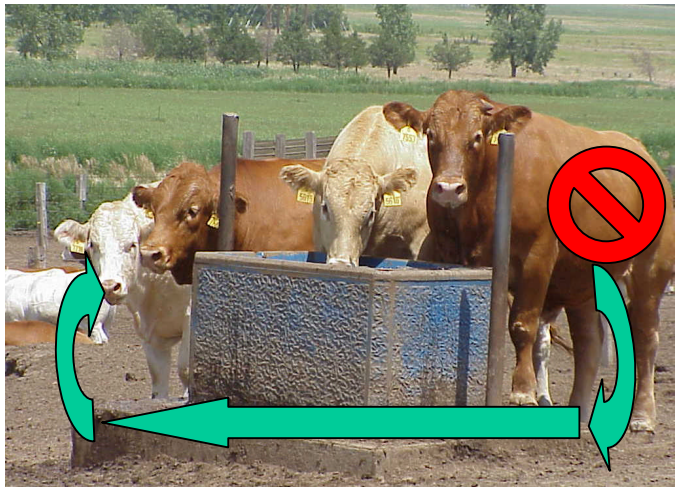
- Vaccinated cattle were 98.3% less likely to be colonized by *E. coli* O157:H7 at the terminal rectum[1]

[1] published in the Journal of Food Protection, November, 2007

Evaluating *E. coli* O157:H7

Scientists agree that a reduction in any of the following parameters will have a positive impact on *E. coli* O157:H7-associated food safety:

- Duration of bacterial shed
- Magnitude of shed
- Colorectal colonization
- Hide contamination
- Pen-level prevalence (ROPES)



- Smith et al. J Food Prot. 2001, 64 (12) 1899-1903.
- Khaitsa et al.J Food Prot 2003, 66 (11) 1972-1977.
- Smith et al. Foodborne Pathogens and Disease. 2005, Vol 2(1): 50-60

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Regulatory Challenges

- *E. coli* O157:H7 does not cause disease in the target animal (cattle).
- The organism has a unique attachment mechanism involving the mucosal surfaces of the GI tract.
- Reduction in the ability of the organism to colonize the GI tract is necessary, with an outcome of reduction in shedding.
- Real need is in field – United States Department of Agriculture (USDA) asked for field efficacy studies – unable to control prevalence in field.

E. coli Vaccine Status

- Bioniche has completed most aspects of develop
  - proof of concept ✔
  - field studies ✔
  - adjuvant withdrawal trial ✔
  - pre-license serials ✔
  - field safety trials ✔

ANIMAL PHARM AWARDS '07 WINNER

"Best new veterinary product for livestock"

A Canadian (CFIA) "conditional license" was granted Dec., 2006

- The Canadian (CFIA) dossier has been accepted and is under review. Discussions are ongoing regarding CFIA's requirements for a full license.

USDA granted eligibility for conditional license Feb., 2008

- For the USDA conditional license, a plan must be set to move to full licensure, one step of manufacture must be in the U.S. and three serial lots produced.
  - With a full U.S. license, product need not be manufactured there.

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Vaccine Market Potential

There are approximately 199 million cattle in North America and Europe (beef cows, dairy cows, calves):

- **North America**
  - 113 million total (approx. 25 million on feedlots)
  - Three doses of vaccine per animal at an estimated $2.00 U.S./dose (higher price expected for non-fed cattle)
- **Europe**
  - 86 million total
  - Three doses of vaccine per animal at an estimated 5-7 Euros/dose
  - Access to the EU will be delayed relative to NA

First commercial vaccine use:
September 21, 2007
Top Meadow Farms
(RR#1 Clarksburg, Ontario, Canada)

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E. coli O157:H7 in the Feedlot

Vaccination of the entire feedlot will have a dramatic effect on *E. coli* cycling in the feedlot and, over time, will decrease the environmental load and subsequent re-infection with each successive cycle.

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E. coli Vaccine Production

A state-of-the-art Animal Health and Food Safety Vaccine Manufacturing Centre is being developed at Bioniche Life Sciences in Belleville, Ontario, Canada:

PHASE ONE

Biocontainment Level II

Capacity: Greater than 40 million doses of *E. coli* O157 vaccine

Online June, 2010

$25 million investment:

- A $10 million repayable loan was provided by the Ontario government
- A $5 million repayable loan was provided by Agriculture Canada
- A $5 million repayable loan was provided by Industry Canada (Industrial Technologies Office)
- A $5 million repayable loan was obtained from the Business Development Bank of Canada

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