

CASE STUDIES: AN INSIDE LOOK AT FOUR COLORADO BIOSCIENCE COMPANIES

BY RACHEL BRAND

TOLMAR

For many Americans, 2008 was a year they hoped for change.

But one Fort Collins company welcomed stability in 2008, as change had been the only constant in the past few years.

With a new owner, desirable product niche and growing market demand, pharmaceutical manufacturer TOLMAR Inc. is on sound footing.

“Right now, TOLMAR is as strong as it has ever been,” CEO Mike Duncan said. “We are owned by a very strong parent company, we have a lot of

capital, and our business has grown dramatically in 2007 and 2008.”

TOLMAR has 15 commercial products: three dental medicines and 12 generic topical dermatology drugs for conditions such as acne and rosacea. All of its products are sold through marketing partners such as Sandoz. The firm researches new dermatology drugs and manufactures its products onsite. It has five Abbreviated New Drug Applications (ANDA) before the U.S. Food and Drug Administration, as well as 15 products in its pipeline.

Privately held TOLMAR does not release sales, but in the past two years its workforce has grown from 144 to 235. That’s quite a contrast from years before.

The turmoil began in 2004 when Atrix Laboratories, also based in Fort Collins, owned the facility.

At the time Atrix was known for its sustained-release drug delivery technology, a polymer gel injected under the skin. Its most successful product was Eligard, a prostate cancer medication.

The 225-employee company also had a small line of dental products, a late-stage acne drug before the FDA, a dermatology research program, and the manufacturing equipment and expertise to develop generic topical dermatology drugs.

When Vancouver, Canada-based drug developer QLT Inc. bought Atrix in late 2004, it promised to spend \$70 million on Atrix’s pipeline.

“We were all very happy about the acquisition,” said Duncan, who has worked at the company since 1996. “We had a huge pipeline, and if we spent all the money necessary to develop it we would have gone into the red.”

Trouble began six months later, largely because of QLT’s flagship product, Visudyne, a treatment for age-related macular degeneration (AMD). First, OSI Pharmaceuticals launched a competitive AMD drug. Then, early results of Genentech’s AMD drug Lucentis, to be marketed in 2006, showed it had greater clinical impact than Visudyne.



As Visudyne’s year-over-year sales fell in late 2005, so did the promise of investing millions of dollars in the Fort Collins pipeline. In December 2006, after Duncan talked to 19 potential buyers, QLT sold the Fort Collins manufacturing plant, dental products line and generic dermatology business to Argentina-based pharmaceutical company Technofarma for \$21 million.

Most venture capitalists Duncan had approached wanted to buy only the generic dermatology line and plant, then resell it two years later for a quick profit.

“Their emphasis is on quick money. But we had a 10-year business model. We said, ‘This company is not going to be profitable for two to five years, and then it is going to be very profitable.’”

Since the acquisition the company is on track to have more than 20 marketed products in the next few years. As for the company’s recent success, Duncan credits Wal-Mart and Target’s decision to sell generics for \$4.

Meanwhile, TOLMAR employees have been working overtime to keep up with demand.



“There is a ton of energy in this place right now,” Duncan said. “We told people we would invest heavily in our pipeline, and we have done that. We told people we would make their job our top priority.”

ACCERA

For patients suffering from Alzheimer’s disease (AD), hope may come from a milkshake-style medicine that feeds hungry brain cells damaged by the disease.

Axona, a medical food product made by Broomfield-based Accera Inc., went on the market in February. The drug targets the metabolic defects and imbalances that characterizing AD, relying on new insights that diabetic-like changes in brain cells’ ability to use sugar play a role in some forms of memory loss. Special fatty acids in Axona offer an alternative food source to starved neurons.

Accera founders Steve Orndorff and Sam Henderson have been pursuing this unorthodox approach for six years, while most companies have been developing drugs that prevent gooey plaques called beta-amyloid from clogging AD patients’ brains.

If successful, Axona will be a home run for the privately held biotech, as well as for its dramatically different approach to AD.

“Both physicians and caregivers tell us, loud and clear, they are desperately seeking drugs with alternative mechanisms,” Orndorff said. “The ones out there today just don’t work.”

Axona causes the liver to act like the patient is starving, producing compounds called ketone bodies. Ketones become the brain’s new energy source. A similar process of ketosis takes place in people on high-protein, low-carb diets.

In a 2007 study of 150 patients with mild-to-moderate AD, taking Axona along with their regular medicines slowed the disease’s progression. Patients given a placebo on top of standard drugs steadily worsened. Axona was only effective in patients who don’t carry the AD gene ApoE4. Still, that’s about half of patients.

AD is incurable, affecting 26 million people globally and about 5 million in the United States alone. The current U.S. market for treatments is an estimated \$4 billion, and the cost of caring for an aging, memory-impaired population is astronomical.

U.S. Food and Drug Administration-approved Axona is marketed as a medical food, available by prescription for \$90 a month. It is intended to be used in addition to traditional therapy.

Medical food is a relatively new category of FDA-regulated “orphan drugs.” Medical foods are formulated to meet distinctive nutritional requirements for particular diseases and must be prescribed and administered under supervision of a physician,

Axona’s active ingredient is a semi-synthetic chemical found in some plants in very small amounts. This chemical has been recognized as safe by the FDA, easing Axona’s approval as a medical food.

Orndorff said he considered pursuing Axona as a traditional pharmaceutical, but the clinical tests would have cost \$600 million to \$800 million and taken 10 years. Developing the product as a medical food has cost \$15 million.

“The medical food route allowed us to get to market faster, cheaper and with much less risk,” he said.

Orndorff founded the company using savings and money from family and friends. Initially Accera was housed at the Fitzsimons Bioscience Incubator in Aurora to save money, and Orndorff took no salary.

When larger investment became critical, he talked to nearly 100 venture capitalists. Finally, he won interest from POSCO BioVentures and Inventages Venture Capital SA. From them and other investors, Accera has raised \$50 million, including a series C round of \$35 million finalized in November 2008.

Orndorff hopes physicians will write 120,000 prescriptions for Axona this year, which translates into \$130 million in revenue.

“We are putting all of our effort into this product, because if it is not successful then our whole business plan is moot,” Orndorff said. “If it works, then we will have money to grow the business, and it validates the mechanism behind the small molecules in our pipeline.”

SANDHILL SCIENTIFIC

Thirteen years ago a world-renowned gastroenterologist mentioned in passing an untested technology involving impedance to a California engineer.

The engineer mulled over the concept with Rick Jory, president of Highlands Ranch-based medical device firm Sandhill Scientific Inc. Jory charged an employee to find out more about impedance. The employee dug up an obscure academic paper and flew to Germany to talk with the researcher.

Because of that chance conversation, today Sandhill Scientific is the world’s leading supplier of impedance technology for



gastroenterologists. Its ZepHr product is the gold standard for diagnosing gastroesophageal acid reflux disease (GERD). And the world-renowned physician, Dr. Donald Castell, gives technical advice to the company.

"I have had phenomenal luck," Jory said. "Still, our motto is, 'to be average is to fail.' We hope we are a world apart from average."

Impedance is the scientific method of measuring changes in resistance to an alternating electrical current when food or other substances, including liquids, pass across metal rings on a catheter.

Although founded in 1981, since licensing impedance technology in 1996, Sandhill's growth has taken off, growing to a 135-employee global company with two GI product lines.

As a privately held company, Sandhill does not reveal financial data, but Jory estimates sales at \$20 million with a compound annual growth rate of 22 percent. Jory attributes the firm's success to a mix of international opportunity hunting and old-fashioned financial management.

With few exceptions, Sandhill has financed its growth through operating cash flow. It has no angel, venture capital or bank investors. "It has required developing a phenomenal level of discipline," Jory said. "If we can't afford something, we don't do it."

About 20 million Americans suffer from acid reflux, characterized by heartburn, chest tightening and nausea. To treat it, doctors routinely ban caffeine and alcohol while prescribing drugs that staunch stomach acid.

If drugs and diet fail, doctors need more information. That's where impedance technology comes in.

The ZepHr combines a disposable catheter probe with a portable recorder as well as analytic software. The probe is inserted into the patient's esophagus, using electrical current to read whether pain is associated with reflux event—either acidic or non-acidic reflux.

"It has revolutionized how we do our particular market niche," Jory said.

A related technology, the Insight, tells doctors if the esophagus is functioning correctly. If not, the patient might benefit from surgery.

Sandhill charges between \$10,000 and \$50,000 for its devices. To push down costs, Sandhill took another risk in 2000: building a manufacturing facility in Prague, Czech Republic. Labor costs fell to \$2 an hour.

"For a small company like ours, this was a big move," Jory said. "But it turned out exceptionally well."

Although the company has no strong competitors, Jory fears hospitals and physician groups may put off purchasing new devices in a poor economy. Increased scrutiny of health-care costs may also come during the new administration.

Sandhill is once again hunting for value. This year the firm will build a plant in Vietnam, cutting labor costs in half. To fund the expansion, managers sacrificed pay increases and bonuses in 2008.

"We have a management team that understands the seriousness of being in business in today's world," Jory said. "We understand our obligation, and we recognize we have to do whatever it takes to make sure we remain viable and healthy."

SOMALOGIC

A Boulder company hopes to launch a diagnostic test this year that can read previously inscrutable signs in patients' blood. SomaLogic's test would make it possible to find disease far

before obvious symptoms such as a lump or pain, making early treatment possible.

Since its founding in 2000 SomaLogic Inc. has raised \$115 million to create medical diagnostics using proteomics. Born of the genomics industry, proteomics is the study of protein levels, instead of genes, to observe health and illness.

Investors include Mitsui & Co. Ltd. and Sumitomo Bakelite Co., Ltd., both of Japan; Switzerland-based Lombard Odier; Maryland-based Skye Associates; France-based Société Générale Asset Management; New Jersey-based ProQuest Investments; and Denver-based NewWest Capital Partners.

The company has partnerships with Boston-based Archemix, Japan's Otsuka Pharmaceutical Co. and Madison, N.J.-based Quest Diagnostics.

"We are interested in ovarian cancer, lung cancer and many cardiovascular diseases," said SomaLogic founder, President and CEO Larry Gold. "These are the diseases—in





general—where a person is asymptomatic until the symptoms get you into the doctor, at which point it is too late.”

Traditional blood tests measure the presence of a single protein, such as human chorionic gonadotropin (hCG) for pregnancy. SomaLogic focuses on finding complicated protein arrangements, also called protein signatures, present in patients who later develop a disease.

To imagine how this might work, consider the recent news coming from Stanford University. Researchers compared the blood of two sets of patients with mild memory loss. Years later some patients developed Alzheimer’s disease, and some didn’t.

The researchers found that 18 signaling proteins predicted with 90 percent accuracy which memory-impaired patients would later develop AD.

“We have gotten blood samples from patients who have certain diseases and those who don’t,” Gold explained. “We have run thousands of experiments just looking for differences. The technology we have developed is simple, now that we have the platform.”

That platform is a method to analyze pro-

teomes—the entire set of proteins in cells. But proteomes are incredibly complex. Proteomes change over time, as cells make different sets of proteins at various times and under different conditions. Heat can change their shape and


make them difficult to recognize, for instance.

The established method of identifying and measuring proteomes employs antibodies, an expensive time-consuming process. SomaLogic uses single-strand nucleic acids called aptamers. These engineered aptamers are the basis for developing a single accurate test for thousands of proteins.

SomaLogic has developed a library of novel aptamers that target more than 500 human proteins along with more than 200 issued and pending patents worldwide. Partners such as Otsuka want to use this resource to validate targets for drug development, drug screening, and diagnostics development.

Due to the complexity of the task at hand, the firm’s scientific development has been slower than hoped, Gold admits. “From January 2000, I told everybody that we were two years away from a product. We have just faced one serious scientific obstacle after another.”

“I can’t help it if molecular biology is hard,” he continued. “We have a wonderful board, and when it was hard, we would say, ‘damn, that was hard, but it was worth doing.’”

Gold, a molecular biology professor at the University of Colorado at Boulder, is well-known in the bioscience arena. In 2007 he won the Colorado BioScience Association’s Lifetime Achievement Award. Prior to SomaLogic, he founded NeXagen Inc., which later became NeXstar Pharmaceuticals Inc. Before forming NeXagen, he founded and served as co-director of research at Synergen Inc., which was acquired by Amgen Inc. 

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