The 22nd Century project: Increasing nicotine to reduce risk—see page 46

CORE COMPETENCIES

Trierenberg's amicable split
A DIFFERENT APPROACH

Biotech firm says increased nicotine levels could be the key to risk reduction.

By Brandy Brinson

Many governments have mandated that cigarette companies lower tar as well as nicotine yields in order to produce “safer” products. The unexpected consequence of this policy is that smokers of lights or ultra-lights may actually increase their tar consumption because of compensation behavior—smoking more cigarettes or inhaling deeper to make up for “lighter” taste. The possibility of maintaining nicotine delivery while significantly reducing tar has not been properly considered. This could even be beneficial as tar is more damaging to human health than nicotine.

Biotech company 22nd Century has developed technology and is working to make nicotine-enriched cigarettes commercially available. The company is now growing tobacco lines that have been genetically modified (GM). The nicotine content of these lines is up to 2.5 times the levels in conventional tobacco. The company envisions its nicotine-enriched tobacco being used in the development of a potential reduced-exposure product (PREP), says Joseph Pandolfino, president of 22nd Century.

Cigarettes on the U.S. market today generally yield 10 to 14 parts tar to 1 part nicotine. 22nd Century intends to reduce tar delivery by developing cigarettes with a tar-to-nicotine ratio of 5 to 7 parts tar to 1 part nicotine.

UP OR DOWN? The public health community has debated for years whether nicotine should be increased or decreased in cigarettes, says Pandolfino. “I believe the rationale for both schools of thought is valid and not contrary whatsoever. Dr. Michael A.H. Russell, a long-term proponent of lowering tar-to-nicotine ratios, presents both sides of the debate in Chapter 15 of Nicotine and Public Health, titled ‘Public Health and Levels of Nicotine: Should Nicotine Levels in Cigarettes be Minimized or Maximized?’”

Despite the anti-tobacco community’s wishes, not all smokers want to quit or will quit. There are three types of smokers—those who would seriously like to quit, those who would moderately like to quit, and those who have no desire to quit.

“Casual research reports that 70 percent of smokers in the U.S. would like to quit; however, the real number is much lower. When surveys ask smokers if a sincere attempt has been made to quit within the last 12 months (such as not smoking for three days or more, using nicotine replacement therapy or other medication), the percentage of serious potential quitters is under 50 percent,” says Pandolfino.

22nd Century wants to develop low yielding tar-to-nicotine ratio cigarettes, produced with nicotine-enriched tobacco, for smokers who have no desire to quit. “Smokers need to have various options available to satisfy their choices, including products to assist them in quitting as well as products that reduce exposure if they choose to continue to smoke,” says Pandolfino.

The growing of GM tobacco is under way. 22nd Century has contracted with two non-affiliated, independent institutions to grow nicotine-enriched flue-cured tobacco in laboratories and greenhouses. Pandolfino says field trials should commence in 2007.
22nd Century is not only developing GM tobacco, but the company also intends to be involved in the design of a PREP. "As pertaining to cigarettes, our company’s goal is to engineer nicotine-enriched tobacco leaf to demonstrate a 'reduced-exposure product' that goes beyond the standard of a PREP. As soon as 22nd Century is satisfied with the quality of its leaf, we will have cigarettes produced that yield tar-to-nicotine ratios of about 5-to-7. Smokers’ reduced exposure to whole tobacco smoke will be evaluated in carefully designed clinical trials," says Pandolfino.

TO THE TEST. Previous research already indicates that the result of lower tar-to-nicotine ratio cigarettes is reduced exposure to whole smoke.

Pandolfino says the company plans to expand these studies to include better design parameters, larger samples of smokers, definitive biomarkers of exposure (such as carboxyhemoglobin) and cigarettes with tar-to-nicotine ratios in the 5-to-7 range that are enjoyable to smokers.

The company has not performed smoking tests with its tobacco. “What we have done, internally and with the assistance of consultants, is thoroughly evaluate all of the available research and data on low tar-to-nicotine ratio cigarettes in journals and within the millions of internal tobacco documents available online. 22nd Century understands where key ratios of tobacco leaf compounds should be for a balanced smoke. The company realizes that producing nicotine-enriched tobacco is not enough. Such tobacco must produce a consumer-acceptable, reduced-exposure cigarette,” says Pandolfino.

Previous experience indicates that cigarettes containing nicotine-enriched tobacco have the potential to produce some harshness. 22nd Century says it has obtained technology to eradicate this.

WHOLE SMOKE. The company believes that reducing a smoker’s daily average dose (DAD) of whole tobacco smoke is more advantageous than only reducing specific smoke constituents. “As deliveries of whole smoke are reduced, virtually all individual smoke compounds are consequentially reduced,” says Pandolfino. Reducing a smoker's DAD of whole smoke will likely reduce the three main groups of smoking-related diseases within a population of smokers—cardiovascular disease, cancer and respiratory disease.

“Also, by enriching leaf nicotine, the scientific realization of reduced exposure to reduced risk can be facilitated by the vast and existing epidemiological record of various dose-response relationships of whole smoke and a number of diseases. It appears that more than just carcinogenic compounds in tobacco smoke need to be reduced to achieve a reduced-risk product. There is no reason why both strategies to reduce risk cannot be utilized in one cigarette. Whole smoke deliveries should be reduced using nicotine-enriched tobacco in conjunction with reducing known carcinogenic smoke compounds by as much as possible.”

TO MARKET. The company is not actively seeking licensees at this time. “I would prefer to bring to market top-quality leaf and a reduced-exposure cigarette that yields tar-to-nicotine ratios of about 5-to-7 with acceptable taste characteristics. I am confident that 22nd Century will achieve these short-term goals. Ultimately, our expectations are to have our cigarettes scientifically accepted as reduced-risk products,” says Pandolfino.

Company representatives did meet twice with a major multinational tobacco company more than a year ago to discuss the licensing of the technology but then decided to pursue product develop-

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22nd Century is the first known company to produce GM nicotine-enriched tobacco for use in cigarettes, but not the first to produce tobacco with enhanced levels of nicotine. In the 1970s, the U.S. Department of Agriculture (USDA) developed tobacco varieties with increased amounts of nicotine for use in 'safer' cigarettes.

The National Cancer Institute’s Smoking and Health Program encouraged the USDA to produce such varieties, according to Dr. Gio Gori. They were created by cross-breeding Nicotiana rustica, a very high-nicotine species, with Nicotiana tabaccum. One particularly successful variety was the high-nicotine Y-1 cultivar developed by Dr. J.F. Chaplin, which was used by British American Tobacco. The downside of Y-1 was that, besides retaining the high nicotine trait from N. rustica, other undesirable traits from N. rustica were also retained, says Pandolfino.

Instead of cross-breeding, 22nd Century uses genetic engineering to increase nicotine levels. Pandolfino says the main advantage of its technology is that it can be performed on any tobacco cultivar used in today’s commercial cigarettes. “This allows desirable traits, such as higher disease resistance, higher crop yields, favorable curing properties and favorable smoke characteristics, to be retained. Also, our company's GM process is substantially faster than the cross-breeding method used to produce Y-1, which took about a decade to create. 22nd Century’s process only takes about 20 months from seed to seed to complete,” he says.

CONTROVERSIAL. Thus far, GM tobacco has been met with great resistance from the tobacco industry. Pandolfino says the tobacco industry should scrutinize how biotechnology has economically benefited the associated industries of GM crops. “About 50 percent of the corn and 85 percent of the soybeans planted in the U.S. are GM. Globally, in 2005, 8.25 million farmers planted over 200 million acres of GM crops. Over the past decade, farmers have increased the acres planted with GM crops by more than 10 percent each year. Sixty-three countries are currently conducting plant biotech research across 57 different crops. China is more GM-friendly than the U.S.

“The reason why there has been explosive growth of GM crops worldwide is simple; biotechnology solves complex problems efficiently. Experts estimate more than one trillion meals containing ingredients from biotech crops have been consumed with no reliable documentation of any food safety issues for people or animals. Twenty-five Nobel Prize winners have expressed their support for plant biotechnology as a ‘powerful and safe’ way to improve agriculture and the environment.”

He says the tobacco industry could significantly benefit from GM tobacco. “Utilizing biotechnology in commercial tobacco varieties (regulating nicotine content aside) could immediately benefit tobacco farmers and consumers. GM tobacco plants would be much less susceptible to various tobacco-plant diseases. Farmers would also enjoy increased crop yields and use less fertilizer and less energy when curing flue-cured tobacco—thus benefiting their pocketbooks and the environment. On the consumer side, GM tobacco could be engineered so that it contains less harmful compounds, including tobacco-specific nitrosamines. GM tobacco would be beneficial for all tobacco stakeholders.”

One of the main fears of the industry is the unintended mixing of traditional tobacco with GM tobacco. Pandolfino says there are many ways to control this, including making GM plants ‘male-sterile,’ topping prior to flowering and maintaining a reasonable distance from non-GM tobacco fields.

He also points out that Philip Morris USA is funding a $17.6 million research project at North Carolina State University (NCSU) to map the tobacco genome. This five-year project is scheduled to conclude in about a year. “In a few years, the function of most tobacco genes will be known. This research will provide extremely powerful tools to commercialize reduced-risk cigarettes. In my opinion, it is only a matter of time before GM tobacco is totally accepted by consumers and the cigarette industry,” Pandolfino predicts.—B.B.
22nd Century is not only producing GM nicotine-enriched tobacco; it has been involved in the production of GM nicotine-free tobacco for several years. The company had its origins in another company, Alternative Cigarettes, Inc. (AC), founded by Pandolfino in 1993. AC is a micro-cigarette company that produces herbal cigarettes. AC eventually learned that its customers were using its nicotine-free herbal cigarettes to quit smoking.

Company executives realized that herbal cigarettes were not likely to ever rival tobacco in terms of taste and aroma characteristics. “We decided to investigate the feasibility of producing tobacco cigarettes that did not contain nicotine. Nicotine-free tobacco cigarettes, we reasoned, had to be more acceptable to consumers than herbal cigarettes,” says Pandolfino.

Philip Morris had previously test marketed nicotine-free tobacco cigarette brands including Next, Merit De-Nic and Benson & Hedges De-Nic. These were produced from a process in which nicotine was extracted from conventional tobacco varieties. Philip Morris invested more than $300 million in these brands, the bulk of which was spent for a nicotine-extraction plant. However, the company eventually pulled the brands from their test markets.

Pandolfino says that in late 1996 he was aware of other GM crops such as corn and decided to investigate whether such techniques could be used to produce GM nicotine-free tobacco. Genetic modification would avoid the costly and complex nicotine-extraction process, and Pandolfino thought it might yield a better-tasting product.

His search led him to molecular biologist Mark A. Conkling at NCSU. Conkling had just cloned a novel gene involved in nicotine biosynthesis. He said that his invention would allow tobacco to grow with virtually no nicotine. Furthermore, the expression of this gene could not only be down-regulated, it could also be up-regulated to increase nicotine.

“This technology was exactly what our company was looking for. Soon after my first conversation with Dr. Conkling, AC signed a research agreement and an exclusive, worldwide license agreement with NCSU to Dr. Conkling’s technology. We also funded international patents pertaining to the technology,” says Pandolfino.

The research turned out to be a success. By late 1998, Conkling had produced tobacco plants that only contained a minute fraction of the nicotine content of regular tobacco—a 98 percent reduction. The plants were normal in every other respect.

“We could now avoid having to build a nicotine-extraction plant. This was critically important for two reasons. First, it would be very costly to build. Second, many believe that additional tobacco flavor is extracted, along with the nicotine, when tobacco is denicotinized in this manner,” says Pandolfino.

The company then had the technology to produce a nicotine-free tobacco cigarette. Pandolfino founded 22nd Century in 1999 and AC assigned all biotechnology assets to the new company. 22nd Century was to be involved exclusively in biotech, while AC would be involved in marketing tobacco products.

**ENTER VECTOR.** Soon after, 22nd Century exclusively sublicensed NCSU’s technology to Vector Tobacco for the reduction of nicotine biosynthesis in traditional tobacco products, including cigarettes, chew and snuff. 22nd Century retained all other rights, including those to enhance nicotine. Vector currently uses the technology in its Quest brand of cigarettes, which is currently sold in eight U.S. states. Quest is the world’s first cigarette consisting of GM tobacco.

Vector Group, during its most recent investor conference call, announced that Quest has recently completed an FDA-approved Phase II clinical trial designed to test the efficacy of Quest cigarettes as a bridge to smoking cessation. Vector Tobacco is currently analyzing the results from this trial and intends to submit a report to the FDA detailing the data. After further discussions with and approval by the FDA, Vector Tobacco hopes to launch a Phase III clinical trial sometime later in 2006.

—B.B.
ment on their own. “After careful consideration, our company believed that we could accelerate the incorporation of our technology into a commercial cigarette on a much shorter timeline with our current business model,” says Pandolfino.

He adds, “I believe there will be considerable interest among the major tobacco companies when our products are shown to be acceptable to smokers and clinical trials demonstrate that reduced exposure to whole tobacco smoke, including tar and carbon monoxide, does indeed occur when nicotine content in tobacco leaf is enhanced.”

The company does envision working with multinationals at some point. “Looking into the future, it is likely that we will enter into a licensing arrangement with a multinational cigarette company that is committed to scientifically establishing that nicotine-enriched cigarettes reduce whole-smoke exposure and ultimately reduce risk. A license would include the right to use our patented gene and related technologies. We could engineer any tobacco variety or allow a company to utilize our gene and do the work themselves,” says Pandolfino. One of 22nd Century’s research groups has recently cloned another novel gene directly involved in alkaloid biosynthesis. 22nd Century has an exclusive worldwide license to this technology and related patent-pending rights.

The company can monitor use of its technology through genetic analysis. Pandolfino explains, “Tobacco can be removed from a cigarette pack and genetically analyzed so any infringers of our intellectual property would be easily identified. That’s what is so valuable about biotech patents in which all rights to a specific gene are protected. Unlike some other types of patents, biotech patents are not easily infringed upon. Our technology is patented in 76 countries and patent-pending in another 16.”

22nd Century is moving forward as rapidly as possible, but it will still be a few years before a product comes to market. Pandolfino says, “Prior to test marketing, 22nd Century will conduct the clinical trials necessary for a thorough science-based evaluation and validation of cigarettes containing nicotine-enriched tobacco. Therefore, I could envision test-marketing products within about three years.”
Most people by now agree that smoking presents a health risk, but debate continues as to what is the best way to reduce that risk. Following the philosophy that the poison is in the dose, product developers have traditionally focused on reducing the compounds of greatest concern—“tar” and nicotine. Thanks to new technologies, the deliveries of these substances in the best-selling U.S. full-flavor brands are down to half of what they were when the smoking-and-health debate started in the 1950s.

But while technology enables cigarette manufacturers to reduce certain tobacco compounds, it doesn’t give them control over smokers’ behaviors. It is difficult to tell to what extent smokers are compensating for reduced deliveries by consuming more cigarettes or drawing larger volumes of smoke into their lungs. At the end of the day, low-tar and low-nicotine cigarettes may or may not be safer than their full-flavor counterparts. Hence the controversy over product descriptors such as “light” and “mild.”

To address this and other issues, a U.S. biotechnology company from Buffalo, New York, is trying something different. Rather than reducing tar and nicotine, 22nd Century wants to reduce only tar, leaving nicotine levels unchanged or even at slightly higher levels than in conventional cigarettes.

The company has started growing tobacco that has been genetically modified to produce nicotine content up to twice the levels of conventional tobacco. Once 22nd Century is pleased with the quality of its leaf, the company intends to produce cigarettes with about 5 parts of tar to 1 part of nicotine—compared with 10-14 parts tar to 1 part of nicotine for a typical cigarette on the U.S. market today.

The underlying thought is that people smoke for nicotine but get sick mainly from tar and harmful gases. Maintaining nicotine levels, says 22nd Century, might give the smoker the satisfaction he craves and eliminate the desire to compensate. The result is a reduction in the smoker’s daily average dose of whole tobacco smoke, which the company believes is more advantageous than only reducing specific smoke constituents.

The project (see article on page 46) is at an early stage, and 22nd Century will have its work cut out for it. Many in the public health community remain skeptical of risk-reduction efforts that focus on anything but smoking cessation, and tinkering with delivery levels could be misinterpreted as nicotine-“spiking,” still a loaded term. On top of this, genetic manipulation is highly controversial in many markets, and established cigarette makers won’t touch it with a 10-foot pole.

Despite the challenges, 22nd Century should be recognized for its efforts. While quitting is indeed the safest option, there will always be a core of people who choose to smoke. For those people, the industry has a responsibility to produce the safest product available. Any attempt to produce such a product should be greeted with enthusiasm, not cynicism.