22nd Century Group, Inc.
Form 10-K
March 18, 2013

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x **Annual Report under Section 13 or 15(d) of the Securities**

Exchange Act of 1934

For the fiscal year ended December 31, 2012

or

¨ **Transitional Report under Section 13 or 15(d) of the**

Securities Exchange Act of 1934

Commission File Number: 000-54111

22nd Century Group, Inc.
(Exact name of registrant as specified in its charter)

Nevada	98-0468420
(State or other jurisdiction of incorporation)	(IRS Employer Identification No.)

9530 Main Street, Clarence, New York 14031
(Address of principal executive offices)

(716) 270-1523

Registrant's telephone number, including area code

Securities registered under Section 12(b) of the Act: None

Securities registered under Section 12(g) of the Act:

Common Stock (Par Value - $0.00001 per share)

Indicate by check mark if the registrant is a well-known seasoned issuer as defined in Rule 405 of the Securities Act

Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Exchange Act.

Yes ¨ No x

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days.

Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Date File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files)

Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer.

Large Accelerated Filer ¨ Accelerated Filer ¨ Non-Accelerated Filer ¨ Smaller Reporting Company x

Indicate by check mark whether the registrant is a shell company (as defined by Rule 12b-2 of the Act).Yes ¨ No x

As of June 29, 2012, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate value of the registrant's common stock (excluding the 18,206,550 shares held by affiliates), based upon the $0.35 price at which such common stock was last sold on June 29, 2012, was approximately $4.7 million.

As of March 7, 2013, there were 38,259,362 shares of Common Stock outstanding.

22nd Century Group, Inc.

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Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements concerning our business, operations and financial performance and condition as well as our plans, objectives and expectations for our business operations and financial performance and condition that are subject to risks and uncertainties. All statements other than statements of historical fact included in this Annual Report on Form 10-K are forward-looking statements. You can identify these statements by words such as “aim,” “anticipate,” “assume,” “believe,” “could,” “due,” “estimate,” “expect,” “goal,” “intend,” “objective,” “plan,” “potential,” “positioned,” “predict,” “should,” “target,” “will,” “would” and other similar expressions that predictions of or indicate future events and future trends. These forward-looking statements are based on current expectations, estimates, forecasts and projections about our business and the industry in which we operate and our management's beliefs and assumptions. These statements are not guarantees of future performance or development and involve known and unknown risks, uncertainties and other factors that are in some cases beyond our control. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected, including:

- Our ability to raise capital or enter into a licensing transaction in order to continue as a going concern;
- Our ability to achieve profitability;
- Our ability to manage our growth effectively;
- Our ability to obtain U.S. Food and Drug Administration (“FDA”) and foreign regulatory approval for our *X-22* smoking cessation product and our Modified Risk Cigarettes;
- Our ability to gain market acceptance for our products;
- Our ability to compete with competitors that may have greater resources than us;
- The potential for our competitors to develop products that are less expensive, safer or more effective than ours;
- Our ability to comply with existing and new government regulations;
- Our ability to retain key personnel;
- The potential exposure to product liability claims, product recalls and other claims;
- The potential for our clinical trials to produce negative or inconclusive results;
- Our ability to adequately protect our intellectual property and to avoid infringement on rights of third parties; and
- Our ability to maintain our rights to our intellectual property licenses.

For the discussion of these risks and uncertainties that could cause actual results to differ materially from those contained in our forward-looking statements, please refer to “Risk Factors” in this Annual Report on Form 10-K. The forward-looking statements included in this Annual Report on Form 10-K are made only as of the date hereof. We undertake no obligation to publicly update or revise any forward-looking statement as a result of new information, future events or otherwise, except as otherwise required by law.

Unless the context otherwise requires, references to the “Company,” “we,” “us,” and “our” refer to 22nd Century Group, Inc., a Nevada corporation, and 22nd Century Limited, LLC, a Delaware limited liability company, as its wholly-owned subsidiary, taken as a whole, and also refer to the operations of 22nd Century Limited, LLC prior to the closing of the merger on January 25, 2011, as described below.

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PART I

Item 1. Business.

Background

22nd Century Group, Inc. was incorporated under the laws of the State of Nevada on September 12, 2005 under the name Touchstone Mining Limited. On January 25, 2011, we entered into a reverse merger transaction with 22nd Century Limited, LLC, which we refer to herein as the Merger. Upon the closing of the Merger, 22nd Century Limited, LLC became our wholly-owned subsidiary. We changed our name to 22nd Century Group, Inc. on November 23, 2010 in anticipation of the Merger with 22nd Century Limited, LLC. After the Merger, we succeeded to the business of 22nd Century Limited, LLC as our sole line of business.

22nd Century Limited, LLC was originally formed as a New York limited liability company on February 20, 1998 as 21st Century Limited, LLC and subsequently merged with a newly-formed Delaware limited liability company, 22nd Century Limited, LLC, on November 29, 1999. Since inception, 22nd Century Limited, LLC has used biotechnology to regulate the nicotine content in tobacco plants.

Overview

22nd Century Limited, LLC ("22nd Century Ltd"), our wholly-owned subsidiary, is a plant biotechnology company focused on tobacco harm reduction and smoking cessation products produced from modifying the nicotine content in tobacco plants through genetic engineering and plant breeding. The Company exclusively controls 107 issued patents and exclusively controls an additional 39 patent applications; of these, we own 12 issued patents plus 22 patent applications and we license on an exclusive basis, 95 issued patents and 17 patent applications. Hercules Pharmaceuticals LLC ("Hercules Pharmaceuticals") and Goodrich Tobacco Company, LLC ("Goodrich Tobacco") are wholly-owned subsidiaries of 22nd Century Ltd. Hercules Pharmaceuticals is focused on *X-22,* a prescription smoking cessation aid currently in development. Goodrich Tobacco is focused on commercial tobacco products and potential modified risk cigarettes.

The Company is primarily involved in the following activities:

- The international licensing of 22nd Century Ltd's technology, proprietary tobaccos, trademarks and brands;

- The development of its *X-22* prescription smoking cessation aid in development;
- The development of its modified risk tobacco products;
- The pursuit of necessary regulatory approvals and clearances at the U.S. Food and Drug Administration (the "FDA") to market *X-22* as a prescription smoking cessation aid and *BRAND A and BRAND B* as Modified Risk Cigarettes in the U.S.;
- The manufacture, marketing and distribution of *RED SUN* and *MAGIC* proprietary cigarettes; and
- The production of *SPECTRUM* research cigarettes for the National Institute on Drug Abuse ("NIDA").

Licensing

The Company has been in discussions with various parties in the tobacco and pharmaceutical industries for licensing its technology and products since the first quarter of 2012. Management is exploring licensing arrangements on a country-by-country basis in the U.S., Europe and Asia. The Company expects to close at least one licensing agreement for its technology and products before the end of the third quarter of 2013.

X-22

The *X-22* therapy protocol utilized in the Company's sponsored Phase II-B clinical trial calls for the patient to smoke our very low nicotine ("VLN") cigarettes over a six-week treatment period to facilitate the goal of the patient quitting smoking by the end of the treatment period. We believe this therapy protocol has been successful in independent clinical trials because VLN cigarettes made from our proprietary tobacco satisfy smokers' cravings for cigarettes while (i) greatly reducing nicotine exposure and nicotine dependence and (ii) extinguishing the association between the act of smoking and the rapid delivery of nicotine. *X-22* involves the same smoking behavior as conventional cigarettes and because patients are simply switching to VLN cigarettes for 6 weeks, *X-22* does not expose the smoker to any new drugs or new side effects. Our Investigational New Drug Application for *X-22*, a kit of VLN cigarettes, was cleared by the FDA in July 2011. Our *X-22* Phase II-B clinical trial was completed in the first quarter of 2012 and did not demonstrate a statistically significant difference in quitting between *X-22* and the active control, a cigarette containing conventional nicotine levels. However, the median number of *X-22* cigarettes smoked during the trial was significantly reduced compared to patients' baseline of usual brand of cigarettes. In evaluating the results of this trial, we believe we may have reduced the nicotine content of *X-22* by too great a percentage, to a level less than half the nicotine content of VLN cigarettes used in various independent smoking-cessation clinical trials that have demonstrated that use of VLN cigarettes increases quit rates.

In contrast to the results of the Company's Phase II-B trial results, independent studies have demonstrated that VLN cigarettes, whether used alone or in conjunction with nicotine replacement therapy (NRT), increase quitting rates. Due to the limited effectiveness and/or serious side effects of existing FDA-approved smoking cessation products, we believe that if additional clinical trials demonstrate increased smoking cessation rates, *X-22* can capture a share of this market by replacing sales and market share from existing smoking cessation aids and expanding the smoking cessation market by encouraging more smokers to attempt to quit smoking. We are currently in the process of identifying potential joint venture partners to fund the remaining *X-22* clinical trials. There is no guarantee that we will (i) obtain the funds necessary to complete additional clinical trials, (ii) identify potential joint venture partners to fund the remaining *X-22* clinical trials, (iii) obtain FDA approval, or (iv) capture significant share of the smoking

cessation market upon FDA approval.

We continue to believe that our VLN cigarettes are effective as a smoking cessation aid. However, we have suspended sponsoring further *X-22* clinical trials pending a complete analysis of results of two independent smoking-cessation trials that were completed in 2012 (ClinicalTrials.gov Identifiers NCT01050569 and NCT01250301), which utilized a different version of our VLN cigarette with a nicotine content similar to those used in previous successful smoking-cessation trials and higher than that used in our own sponsored Phase II-B trial. A portion of the results of these two trials has been disclosed at the annual meeting of the Society for Research on Nicotine and Tobacco ("SRNT") held in Boston on March 13 to 16, 2013.

Regarding the NCT01050569 clinical trial, results only in terms of gender differences in abstinence rates were disclosed at the SRNT annual meeting. Dorothy Hatsukami, PhD, was principal investigator of the study. Within the female population at the end of treatment (week 12), the group assigned our VLN cigarette had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned a 21mg nicotine patch. Within the male population at the end of treatment (week 12), the group assigned a 21mg nicotine patch had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned our VLN cigarette.

Regarding the NCT01250301 clinical trial, certain results were disclosed in a presentation at the SRNT annual meeting given by Hayden McRobbie, Ph.D. of Queen Mary University of London, Wolfson Institute of Preventative Medicine, who was the principal investigator of the study. Pfizer Inc. was also a collaborator of the study. This clinical trial evaluated whether the use of our VLN cigarette in combination with Chantix® or in combination with nicotine replacement therapy ("NRT") increases abstinence rates over the use of Chantix® or the use of NRT. The study included one hundred smokers who were prescribed varenicline (trademarked Chantix, or Champix outside the U.S.) and one hundred smokers who were prescribed NRT. Half the smokers of each of these groups were randomly selected to also use our VLN cigarettes for the first 2 weeks of treatment. All smokers received 9 weekly behavioral support sessions throughout the 12-week study period. The group that used our VLN cigarettes had a 70% quit rate one week after stopping VLN cigarette use compared to a 53% quit rate of the group not using VLN cigarettes after week 1 (p=0.02). The group that used our VLN cigarettes had a 64% four-week continuous abstinence rate during weeks 3 to 6 compared to a 50% four-week continuous abstinence rate during weeks 1 to 4 (p=0.06). Quit rates at 12 weeks post treatment were not reported in the presentation.

The full set of results of these 2 independent clinical trials are expected to be published in peer reviewed journals and will be compared to results of other independent clinical trials of our VLN cigarettes and results of our Phase II-B trial to determine which variables optimize cessation. One preliminary hypothesis, in conjunction with results of various other studies of our VLN cigarettes, is that having two types of prescription VLN cigarettes available may be advantageous for increased smoking cessation in the general population; one having a higher nicotine content than the other. Upon identifying a suitable joint venture partner to fund further *X-22* clinical trials, we will then request a meeting with the U.S. Food and Drug Administration ("FDA"), and thereafter we may resume our own sponsored *X-22* clinical trials.

Potential Modified Risk Cigarettes and the Tobacco Control Act

The 2009 Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act") granted the FDA authority over the regulation of all tobacco products. While it prohibits the FDA from banning cigarettes outright, it allows the FDA to require the reduction of nicotine or any other compound in tobacco and cigarette smoke. The Tobacco Control Act also banned all sales in the U.S. of cigarettes with characterizing flavors (other than menthol). As of June 2010, all cigarette companies were required to cease the use of the terms "low tar," "light" and "ultra light" in describing cigarettes sold in the U.S. Besides numerous other regulations, including certain marketing restrictions, for the first time in history, a U.S. regulatory agency will scientifically evaluate cigarettes that may pose lower health risks as compared to conventional cigarettes.

The Tobacco Control Act establishes procedures for the FDA to regulate the labeling and marketing of modified risk tobacco products, which includes cigarettes that (i) reduce exposure to tobacco toxins and (ii) are reasonably likely to pose lower health risks as compared to conventional cigarettes ("Modified Risk Cigarettes"). The Tobacco Control Act requires the FDA to issue specific regulations or guidance regarding applications that must be submitted to the FDA

for the authorization to label and market Modified Risk Cigarettes. On March 30, 2012, the FDA issued *Modified Risk Tobacco Product Applications Draft Guidance.*

We believe that two types of our cigarettes in development which we refer to as *BRAND A* and *BRAND B*, may qualify as Modified Risk Cigarettes. Compared to commercial cigarettes, the tobacco in *BRAND A* has approximately 95% less nicotine than tobacco in cigarettes previously marketed as "light" cigarettes, and *BRAND B*'s smoke contains an extraordinary low amount of "tar" per milligram of nicotine.

Within our two product categories, the Tobacco Control Act offers us the following specific advantages:

Smoking Cessation Aids

FDA approval must be obtained, as has been the case for decades, before a product can be marketed for quitting smoking. The Tobacco Control Act provides that products for quitting smoking or smoking cessation, such as *X-22*, be considered for "Fast Track" designation by the FDA. The "Fast Track" programs of the FDA are intended to facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach the market expeditiously. We believe that upon completion of a company-sponsored clinical trial demonstrating efficacy, *X-22* will qualify for "Fast Track" designation by the FDA. However, there is no guarantee that the FDA will grant "Fast Track" designation to *X-22*. Please see page 17 for a further discussion on the FDA's "Fast Track" program.

Modified Risk Cigarettes

We intend to seek FDA authorization to market *BRAND A* and *BRAND B* as Modified Risk Cigarettes. We believe that *BRAND A* and *BRAND B* will achieve significant market share in the global cigarette market among smokers who will not quit but are interested in reducing the harmful effects of smoking. There is no guarantee that we will obtain FDA authorization to market *BRAND A* and *BRAND B* as Modified Risk Cigarettes or that we will achieve a significant market share of this specified subgroup of smokers. We believe this new regulatory environment represents a paradigm shift for the tobacco industry. The Tobacco Control Act allows the FDA to mandate the use of reduced-risk technologies across all conventional tobacco products or cigarettes. We believe the Tobacco Control Act may create opportunities for us to license our proprietary technology and/or tobaccos to larger competitors. We will need significant additional capital to complete the FDA authorization process for our Modified Risk Cigarettes. The amount of capital is currently unknown since it is uncertain how many exposure studies the FDA will require for *BRAND A* and *BRAND B*.

Tar, Nicotine, and Smoking Behavior

The dependence of many smokers on tobacco is largely due to the properties of nicotine, but the adverse effects of smoking on health are mainly due to other components present in tobacco smoke, including “tar” and carbon monoxide. “Tar” is the common name for the (resinous) total particulate matter minus nicotine and water produced by the burning of tobacco (or other plant material) during the act of smoking. “Tar” and nicotine are commonly measured in milligrams per cigarette trapped on a Cambridge filter pad under standardized conditions using smoking machines. These results are referred to as “yields” or, more specifically, “tar” yield and nicotine yield.

Individual smokers generally seek a certain amount of nicotine per cigarette and can easily adjust how intensely each cigarette is smoked to obtain a satisfactory amount of nicotine. Smoking of low yield (“light” or “ultra light”) cigarettes compared to high yield (“full flavor”) cigarettes often results in taking more puffs per cigarette, larger puffs and/or smoking more cigarettes per day to obtain a satisfactory amount of nicotine, a phenomenon known as “compensation” or “compensatory smoking.” A report by the National Cancer Institute in 2001 stated that due to compensatory smoking, low yield cigarettes are not safer than full flavor cigarettes, which is the reason that the Tobacco Control Act has banned the use of the terms “low tar,” “light” and “ultra light” in the U.S. market. Studies have shown, however, that smokers generally do not compensate when smoking cigarettes made with our VLN tobacco, and that smoking VLN cigarettes, such as *BRAND A,* actually assist smokers to smoke fewer cigarettes per day and reduce their exposure to “tar” and nicotine. Other studies have demonstrated that compensatory smoking (e.g., more and/or larger puffs per cigarette) of low-tar research cigarettes, similar to *BRAND B (*though *BRAND B* was not used in such studies), is greatly curtailed resulting in smokers inhaling less “tar” and carbon monoxide. Additional studies will be necessary to establish whether *BRAND B* cigarettes achieve similar results.

RED SUN and MAGIC Cigarettes

Our subsidiary, Goodrich Tobacco, introduced two super-premium priced cigarette brands, *RED SUN* and *MAGIC*, into the U.S. market in the first quarter 2011. Both brands are available in regular and menthol and all brand styles are king size and packaged in hinge-lid hard packs. Goodrich Tobacco has thus far had its cigarette brands contract manufactured by a non-participating manufacturer to the MSA. On January 23, 2013, Goodrich Tobacco applied to the Alcohol and Tobacco Tax Trade Bureau ("TTB") for a federal permit to manufacture its own tobacco products. Being a federally licensed tobacco product manufacturer is a primary requirement of becoming a participating manufacturer of the "Master Settlement Agreement" or "MSA," a settlement among 46 states and the tobacco industry administered by the National Association of Attorneys General ("NAAG"). On February 26, 2013, Goodrich Tobacco applied to the NAAG to become a participating manufacturer to the MSA. Both of these measures, if approved by the TTB and NAAG, will greatly facilitate the sales and distribution potential of *RED SUN* and *MAGIC*.

SPECTRUM Government Research Cigarettes

As a subcontractor to RTI International ("RTI") in RTI's contract with The National Institute on Drug Abuse for the Research Cigarette Option, we supply modified nicotine (from very low to high) cigarettes to NIDA. These research cigarettes are distributed under the mark *SPECTRUM*.

Market

Cigarettes and Smoking Cessation Aids

Our products address unmet needs of smokers; for those who want to quit, an innovative smoking cessation aid, and for those who do not quit, cigarettes that can reduce the level of exposure to tobacco toxins.

According to the U.S. Center for Disease Control (CDC), the U.S. cigarette market consists of approximately 45 million adult smokers who spent approximately $80 billion in 2011 on approximately 300 billion cigarettes. Worldwide manufacturer sales in 2011 were over 5.0 trillion cigarettes, resulting in annual retail sales of approximately $610 billion. In 2010, annual manufacturer sales of smoking cessation aids in the U.S., all of which must be approved by the FDA, were approximately $1.0 billion. Outside the United States, the smoking cessation market is in its infancy and is approximately $3.0 billion.

Approximately 50% of U.S. smokers attempt to quit smoking each year, but only 2% to 5% actually quit smoking in a given year. It takes smokers an average of 8 to 11 "quit attempts" before achieving long-term success. Approximately 95% of "self-quitters" (i.e., those who attempt to quit smoking without any treatment) relapse and resume smoking. The Institute of Medicine, the health arm of the National Academy of Sciences, in a 2007 report concludes: "There is an

enormous opportunity to increase population prevalence of smoking cessation by reaching and motivating the 57 percent of smokers who currently make no quit attempt per year." We believe that our *X-22* smoking cessation aid will be attractive to smokers who have been frustrated in their previous attempts to quit smoking using other therapies.

Use of existing smoking cessation aids results in relapse rates that can be as high as 90% in the first year after a smoker initially "quits." Smokers currently have the following limited choices of FDA-approved products to help them quit smoking:

- varenicline (Chantix®/Champix® outside the U.S.), manufactured by Pfizer,
- bupropion (Zyban®), manufactured by GlaxoSmithKline, and
- nicotine replacement therapy, or "NRT," which is available in the U.S. in several forms: gums, patches, nasal sprays, inhalers and lozenges.

Chantix® and Zyban® are pills and are nicotine free. Chantix®, Zyban®, the nicotine nasal spray and the nicotine inhaler are available by prescription only. Nicotine gums, nicotine patches, and lozenges are available over-the-counter.

Chantix® was introduced in the U.S. market in the fourth quarter 2006. Since 2007, Chantix® has been the best-selling smoking cessation aid in the United States, with sales, according to Pfizer Inc., of $701 million in 2007, $489 million in 2008, $386 million in 2009, $330 million in 2010 and $326 million in 2011. In July 2009, the FDA required a "Boxed Warning," the most serious type of warning in prescription drug labeling, for both Chantix® and Zyban® based on the potential side effects of these drugs. Despite this Boxed Warning, worldwide sales of Chantix® in 2009 to 2011 were approximately $700 million, $755 million, and $720 million, respectively.

Other than Chantix® and Zyban®, the only FDA-approved smoking cessation therapy in the United States is NRT. These products consist of gums, patches, nasal sprays, inhalers and lozenges. Nicotine gums and nicotine patches have been sold in the U.S. for approximately 28 years and 20 years, respectively, and millions of smokers have already tried NRT products and failed to stop smoking due to the limited effectiveness of these products. According to Perrigo Company, a pharmaceutical company that sells NRT products, retail sales of NRT products in the United States were $800 million in the fiscal year ended June 30, 2012.

Modified Risk Tobacco Products

A substantial number of adult smokers are unable or unwilling to quit smoking. For example, each year one-half of the adult smokers in the United States do not attempt to quit. Nevertheless, we believe the majority of these smokers are interested in reducing the harmful effects of smoking.

In a 2005 analyst report, *The Third Innovation, Potentially Reduced Exposure Cigarettes*, JP Morgan examined the effects of FDA regulation of tobacco, including the market for safer cigarettes. JP Morgan's proprietary survey of over 600 smokers found that 90% of smokers are willing to try a safer cigarette. Among JP Morgan's other conclusions, it stated: "FDA oversight would imbue PREPS ['potential reduced exposure products' which essentially equate to potential modified risk tobacco products] with a regulatory 'stamp of approval' and allow for more explicit comparative health claims with conventional cigarettes. Consumers should trust the FDA more than industry health claims." Prior to the Tobacco Control Act becoming law in 2009, no regulatory agency or body had the authority to assess potential modified risk tobacco products.

Some major cigarette manufacturers have developed and marketed alternative cigarette products. For example, Philip Morris USA developed an alternative cigarette, called Accord®, in which the tobacco is heated rather than burned. R.J. Reynolds Tobacco Company has developed and is marketing an alternative cigarette, called Eclipse®, in which the tobacco is primarily heated, with only a small amount of tobacco burned. Philip Morris and RJ Reynolds have indicated that their products may deliver fewer smoke components compared to conventional cigarettes. Vector Tobacco Inc. ("Vector Tobacco"), which is our former licensee, has marketed a cigarette offered in three brand styles with reduced levels of nicotine, called Quest®. Both Accord® and Eclipse®, which are not conventional cigarettes (e.g., referred to as "heat not burn" products since they do not burn down) and have only achieved limited sales. With the exception of Eclipse®, the above products are no longer being manufactured.

Complete cessation from all tobacco and medicinal nicotine products is the ultimate goal of the public health community. However, some public health officials desire to migrate cigarette smokers en masse to medicinal nicotine (also known as NRT) or smokeless tobacco products to replace cigarettes. We believe this is unattainable in the foreseeable future for many reasons, including because the smoking experience is much more complex than simply seeking nicotine. In a 2009 WHO report, statistics demonstrate that approximately 90% of global tobacco users smoke cigarettes. Worldwide cigarette sales (in U.S. dollars) are approximately 12 times greater than sales of smokeless tobacco products and approximately 200 times greater than sales of NRT products. Although a small segment of the smoking population is willing to use smokeless tobacco products in conjunction with cigarettes (known as dual users), a large percentage of smokers is not interested in using smokeless tobacco products exclusively.

There are newer forms of smokeless tobacco products that have been introduced in the market that are less messy to use than chewing tobacco or dry snuff (since spitting is not involved). These products include Swedish-style snus and dissolvable tobacco products such as Ariva® and Stonewall® tablets made by Star Scientific Inc., and Camel® Orbs, Camel® Strips and Camel® Sticks recently introduced by R.J. Reynolds Tobacco Company. Although use of such products may be more discreet and convenient than traditional forms of smokeless tobacco, they have the same route of delivery of nicotine as nicotine gum and nicotine lozenges, which have been available over-the-counter in the United States for approximately 28 years and 10 years, respectively, and have not significantly replaced cigarettes.

Products

X-22 Smoking Cessation Aid

X-22 is a tobacco-based botanical medical product for use as a smoking cessation therapy. Upon U.S. Food and Drug Administration ("FDA") approval, *X-22* will be a prescription-only kit containing VLN cigarettes made from our proprietary tobacco, which has approximately 95% less nicotine compared to tobacco in existing "light" cigarettes. The *X-22* therapy protocol calls for the patient to smoke our VLN cigarettes over a six-week treatment period to facilitate the goal of the patient quitting smoking by the end of the treatment period. We believe this therapy protocol has been successful in independent clinical trials because VLN cigarettes made from our proprietary tobacco satisfy smokers' cravings for cigarettes while (i) greatly reducing nicotine exposure and nicotine dependence and (ii) extinguishing the association between the act of smoking and the rapid delivery of nicotine.

Our Investigational New Drug Application for *X-22*, a kit of very low nicotine ("VLN") cigarettes, was cleared by the FDA in July 2011. Our *X-22* Phase II-B clinical trial was completed in the first quarter of 2012 and did not demonstrate a statistically significant difference in quitting between *X-22* and the active control, a cigarette containing conventional nicotine levels. In evaluating the results of this trial, we believe we may have reduced the nicotine content of *X-22* by too great a percentage, to a level less than half the nicotine content of VLN cigarettes used in various independent smoking-cessation clinical trials that have demonstrated that use of VLN cigarettes increases quit rates.

Partial results of two independent smoking-cessation clinical trials that were completed in 2012 (ClinicalTrials.gov Identifiers NCT01050569 and NCT01250301) have been disclosed at the annual meeting of the Society for Research on Nicotine and Tobacco ("SRNT") held in Boston on March 13 to 16, 2013.

1. University of Minnesota Masonic Cancer Center - Phase II - 235 subjects

·Follow-up study to Hatsukami et al. 2010
·ClinicalTrials.gov Identifier: NCT01050569
· Evaluating quitting results of six-week treatment period among 3 groups:
(i) exclusive use of a VLN cigarette (a VLN cigarette with slightly higher nicotine content than those used in the 22nd Century trial);

(ii) 21-mg nicotine patch; and

(iii) concurrent use of VLN cigarette and nicotine patch

·Trial included a 6-month follow-up period

2. Queen Mary University of London, in collaboration with Pfizer - 200 subjects

·Same VLN cigarette utilized in above study
·ClinicalTrials.gov Identifier: NCT01250301
· Evaluating whether the use of a VLN cigarette in combination with Chantix® (or NRT) increases quitting over use of Chantix® (or NRT) alone
·Chantix® is branded as Champix® outside the United States

Regarding the NCT01050569 clinical trial, results only in terms of gender differences in abstinence rates were disclosed at the SRNT annual meeting. Dorothy Hatsukami, PhD, was principal investigator of the study. Smokers were randomly assigned (n=235) to one of three treatment groups: (i) our VLN cigarette (n=79); (ii) a 21mg nicotine patch (n=80) or (iii) a combination of the 21mg nicotine patch and our VLN cigarette (n=76). Each group received 6 weeks of treatment, an additional 6 weeks of behavioral treatment and 3 follow-up visits. Tobacco and nicotine use self-report and carbon monoxide (CO) were assessed at each visit. Urinary cotinine was assessed at baseline and at weeks 2, 6, 12, 24 and 36. CO and cotinine verified continuous abstinence rates at end of treatment (week 12) varied significantly by treatment group and gender (p=0.029 for the interaction). Within the female population at the end of treatment (week 12), the group assigned our VLN cigarette had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned a 21mg nicotine patch. Within the male population at the end of treatment (week 12), the group assigned a 21mg nicotine patch had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned our VLN cigarette.

Regarding the NCT01250301 clinical trial, certain results were disclosed in a presentation at the SRNT annual meeting given by Hayden McRobbie, Ph.D. of Queen Mary University of London, Wolfson Institute of Preventative Medicine, who was the principal investigator of the study. Pfizer Inc. was also a collaborator of the study. This clinical trial evaluated whether the use of our VLN cigarette in combination with Chantix® or in combination with nicotine replacement therapy (“NRT”) increases abstinence rates over the use of Chantix® or the use of NRT. The study included one hundred smokers who were prescribed varenicline (trademarked Chantix, or Champix outside the U.S.) and one hundred smokers who were prescribed NRT. Half the smokers of each of these groups were randomly selected to also use our VLN cigarettes for the first 2 weeks of treatment. All smokers received 9 weekly behavioral support sessions throughout the 12-week study period. The group that used our VLN cigarettes had a 70% quit rate one week after stopping VLN cigarette use compared to a 53% quit rate of the group not using VLN cigarettes after week 1 (p=0.02). The group that used our VLN cigarettes had a 64% four-week continuous abstinence rate during weeks 3 to 6 compared to a 50% four-week continuous abstinence rate during weeks 1 to 4 (p=0.06). Quit rates at 12 weeks post treatment were not reported in the presentation.

RED SUN and MAGIC Cigarettes

Our subsidiary, Goodrich Tobacco, introduced two super-premium priced cigarette brands, *RED SUN* and *MAGIC*, into the U.S. market in the first quarter 2011. Both brands are available in regular and menthol and all brand styles are king size and packaged in hinge-lid hard packs. In the second quarter of 2013, we intend to focus our marketing efforts on tobacconists, smoke shops and tobacco outlets in the U.S. The ban in 2009 by the FDA of all cigarettes with characterizing flavors (with the exception of menthol) has resulted in a product void in these specialty tobacco channels for super-premium priced products. We believe that certain U.S. cigarette wholesalers and retailers will carry our brands, among other reasons, to increase their margins.

SPECTRUM Government Research Cigarettes

As a subcontractor to RTI International ("RTI") in RTI's contract with The National Institute on Drug Abuse for the Research Cigarette Option, we supply modified nicotine (from very low to high) cigarettes to NIDA. These research cigarettes are distributed under the mark *SPECTRUM*.

Our Modified Risk Cigarettes

We believe that our *BRAND A* and *BRAND B* cigarettes will benefit smokers who are unable or unwilling to quit smoking and who may be interested in cigarettes which reduce exposure to certain tobacco smoke toxins and/or pose a lower health risk than conventional cigarettes. This includes the approximate one-half of the 45 million adult smokers in the United States who do not attempt to quit in a given year. Compared to commercial cigarettes, the tobacco in *BRAND A* has approximately 95% less nicotine than tobacco in cigarettes previously marketed as "light" cigarettes and *BRAND B*'s smoke contains an extraordinary low amount of "tar" per milligram of nicotine. We believe that *BRAND A* and *BRAND B* will qualify as Modified Risk Cigarettes and we intend to seek FDA authorization to market *BRAND A* and *BRAND B* as Modified Risk Cigarettes. On March 30, 2012, the FDA issued *Modified Risk Tobacco Product Applications Draft Guidance*, which we will utilize to file our two modified risk applications with the FDA. We will need significant additional capital to complete the FDA authorization process for our Modified Risk Cigarettes. The amount of capital is currently unknown since it is uncertain how many exposure studies the FDA will require for *BRAND A* and *BRAND B*.

BRAND A Cigarettes

Compared to commercial tobacco cigarettes, *BRAND A* has the lowest nicotine content. The tobacco in *BRAND A* contains approximately 95% less nicotine than tobacco in leading "light" cigarette brands. Clinical studies have demonstrated that smokers who smoke VLN cigarettes containing our proprietary tobacco smoke fewer cigarettes per day resulting in significant reductions in smoke exposure, including "tar," nicotine and carbon monoxide. Due to the very low nicotine levels, compensatory smoking does not occur with VLN cigarettes containing our proprietary tobacco (Hatsukami et al. 2010).

In a June 16, 2010 press release, Dr. David Kessler, the former FDA Commissioner, recommended that "[t]he FDA should quickly move to reduce nicotine levels in cigarettes to non-addictive levels. If we reduce the level of the stimulus, we reduce the craving. It is the ultimate harm reduction strategy." Shortly thereafter in a Washington Post article, Dr. Kessler said that the amount of nicotine in a cigarette should drop from about 10 milligrams to less than 1 milligram. *BRAND A* contains approximately 0.7 milligram of nicotine per cigarette.

A Phase II smoking cessation clinical trial at the University of Minnesota Masonic Comprehensive Cancer Center (Hatsukami et al. 2010) also measured exposure of various smoke compounds in smokers from smoking a VLN cigarette containing our proprietary tobacco over a six (6)-week period. Smokers significantly reduced their smoking as compared to their usual brand of cigarettes. The number of VLN cigarettes smoked per day on average decreased from 19 (the baseline number of cigarettes of smokers' usual brand) to 12 by the end of the six (6)-week period, even though participants were instructed to smoke ad libitum (as many cigarettes as desired) during treatment. Furthermore, besides significant reductions in other biomarkers, carbon monoxide (CO) levels, an indicator of smoke exposure, significantly decreased from 20 parts per million (baseline) to 15 parts per million. Cotinine, a metabolite and

biomarker of nicotine, significantly decreased from 4.2 micrograms/mL (baseline) to 0.2 micrograms/mL. All differences were statistically significant (P<0.05).

We believe these and other results and future exposure studies the FDA may require will result in a modified risk cigarette claim for *BRAND A*. We further believe smokers who desire to smoke fewer cigarettes per day while also satisfying cravings and reducing exposure to nicotine will find *BRAND A* beneficial. There is no guarantee that *BRAND A* will be classified as a Modified Risk Cigarette by the FDA.

BRAND B Cigarettes

Using a proprietary high nicotine tobacco blend in conjunction with specialty cigarette components, *BRAND B* allows the smoker to achieve a satisfactory amount of nicotine per cigarette while inhaling less “tar” and carbon monoxide. At the same time, we do not expect exposure to nicotine from *BRAND B* to be significantly higher than some commercially available full flavor cigarette brands. We believe smokers who desire to reduce smoke exposure but are less concerned about nicotine will find BRAND B beneficial. *BRAND B* has a “tar” yield between typical “light” and “ultra-light” cigarettes, but a nicotine yield of typical full flavor cigarettes.

In a 2001 report, entitled *Clearing the Smoke, Assessing the Science Base for Tobacco Harm Reduction*, the Institute of Medicine notes that a low “tar”/moderate nicotine cigarette is a viable strategy for reducing the harm caused by smoking. The report states: “Retaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco is another general strategy for harm reduction.” We believe that evaluation of *BRAND B* in short-term human exposure studies will confirm that exposure to smoke, including certain tobacco smoke toxins and carbon monoxide, is significantly reduced when smoking *BRAND B* as compared to smoking the leading brands of cigarettes. We believe results from these exposure studies will warrant a modified risk claim for *BRAND B*. There is no guarantee that *BRAND B* will be classified as a Modified Risk Cigarette by the FDA.

Smoking Cessation Clinical Trials with VLN Cigarettes

Partial results of two independent smoking-cessation clinical trials that were completed in 2012 (ClinicalTrials.gov Identifiers NCT01050569 and NCT01250301) have been disclosed at the annual meeting of the Society for Research on Nicotine and Tobacco ("SRNT") held in Boston on March 13 to 16, 2013.

Regarding the NCT01050569 clinical trial, results only in terms of gender differences in abstinence rates were disclosed at the SRNT annual meeting. Dorothy Hatsukami, PhD, was principal investigator of the study. Smokers were randomly assigned (n=235) to one of three treatment groups: (i) our VLN cigarette (n=79); (ii) a 21 mg nicotine patch (n=80) or (iii) a combination of the 21 mg nicotine patch and our VLN cigarette (n=76). Each group received 6 weeks of treatment, an additional 6 weeks of behavioral treatment and 3 follow-up visits. Tobacco and nicotine use self-report and carbon monoxide ("CO") were assessed at each visit. Urinary cotinine was assessed at baseline and at weeks 2, 6, 12, 24 and 36. CO and cotinine verified continuous abstinence rates at end of treatment (week 12) varied significantly by treatment group and gender (p=0.029 for the interaction). Within the female population at the end of treatment (week 12), the group assigned our VLN cigarette had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned a 21mg nicotine patch. Within the male population at the end of treatment (week 12), the group assigned a 21mg nicotine patch had the highest continuous abstinence rate; the group assigned concurrent use of our VLN cigarette with a 21mg nicotine patch had the next highest continuous abstinence rate followed by the group assigned our VLN cigarette.

Regarding the NCT01250301 clinical trial, certain results were disclosed in a presentation at the SRNT annual meeting given by Hayden McRobbie, Ph.D. of Queen Mary University of London, Wolfson Institute of Preventative Medicine, who was the principal investigator of the study. Pfizer Inc. was also a collaborator of the study. This clinical trial evaluated whether the use of our VLN cigarette in combination with Chantix® or in combination with nicotine replacement therapy ("NRT") increases abstinence rates over the use of Chantix® or the use of NRT. The study included one hundred smokers who were prescribed varenicline (trademarked Chantix, or Champix outside the U.S.) and one hundred smokers who were prescribed NRT. Half the smokers of each of these groups were randomly selected to also use our VLN cigarettes for the first 2 weeks of treatment. All smokers received 9 weekly behavioral support sessions throughout the 12-week study period. The group that used our VLN cigarettes had a 70% quit rate one week after stopping VLN cigarette use compared to a 53% quit rate of the group not using VLN cigarettes after week 1 (p=0.02). The group that used our VLN cigarettes had a 64% four-week continuous abstinence rate during weeks 3 to 6 compared to a 50% four-week continuous abstinence rate during weeks 1 to 4 (p=0.06). Quit rates at 12 weeks post treatment were not reported in the presentation.

Previous to the 2 clinical Trials presented at the 2013 SRNT meeting, VLN cigarettes containing our proprietary tobacco have been the subject of various independent studies, including two Phase II clinical trials for smoking cessation which were not funded by us. Both of these Phase II clinical trials were "intent to treat" trials, meaning that any patients who dropped out of the trials for any reason at any time during treatment or during the follow-up periods were considered failures (still smoking and not abstinent). Dropout rates during smoking cessation trials are generally

high since patients either quit smoking or resume smoking their usual brand. In either case, they may believe there is no reason to continue.

One of these two Phase II clinical trials compared the quitting efficacy of a VLN cigarette containing our proprietary tobacco versus a low nicotine cigarette and an FDA-approved nicotine lozenge (4 mg) in a total of 165 patients treated for six (6) weeks (Hatsukami *et al.* 2010, *Addiction* 105:343–355). This clinical trial was led by Dr. Dorothy Hatsukami at the University of Minnesota Masonic Comprehensive Cancer Center. Dr. Hatsukami was selected in 2010 as one of the nine voting members of the 12-person Tobacco Products Scientific Advisory Committee ("TPSAC"), within the FDA's Center for Tobacco Products created under the Tobacco Control Act. (TPSAC will make recommendations and issue reports to the FDA Commissioner on tobacco regulatory matters, including but not limited to, the impact of the use of menthol in cigarettes, altering levels of nicotine in tobacco products, and applications submitted to the FDA for modified risk tobacco products.)

Results from this Phase II trial conclude that patients exclusively using the VLN cigarette containing our proprietary tobacco achieved a 43% quit rate (confirmed four (4)-week continuous abstinence) as compared to a quit rate of 35% for the group exclusively using the FDA-approved nicotine lozenge and a 21% quit rate for the group exclusively using the low nicotine cigarette. Smoking abstinence at the 6-week follow-up after the end of treatment was 47% for the VLN cigarette group, 37% for the nicotine lozenge group and 23% for the low nicotine cigarette group. Furthermore, the VLN cigarette was also associated with greater relief from withdrawal symptoms and cravings of usual brand cigarettes than the nicotine lozenge. Carbon monoxide (CO) levels in patients were tested at each treatment clinic visit to verify smoking abstinence.

Unlike Phase III clinical trials for other FDA-approved smoking cessation aids, four (4) week continuous abstinence in the University of Minnesota Phase II trial was measured after the treatment period, when patients were "off" medication, rather than during the last four weeks of the treatment period. For example, according to the prescription Chantix® label, four (4)-week continuous abstinence in the Chantix® Phase III clinical trials (the 44 percent quit rate advertised by Pfizer) was measured during the last four weeks of the 12-week treatment period, while patients were still taking Chantix®. In one of these Chantix® Phase III clinical trials, approximately one-third of those who had been abstinent during the last week of treatment returned to smoking within four weeks after they stopped taking Chantix®, and approximately 45% returned to smoking within eight weeks after they stopped taking Chantix®.

Patients who used the VLN cigarette over the six (6)-week treatment period significantly reduced their smoking as compared to their usual brand of cigarettes. The number of VLN cigarettes smoked per day on average decreased from 19 (the baseline number of cigarettes of the smoker's usual brand) to 12 by the end of the six (6)-week treatment period, even though participants in this clinical trial were instructed to smoke ad libitum (as many cigarettes as desired) during treatment. Carbon monoxide (CO) levels, an indicator of smoke exposure, significantly decreased from 20 parts per million (baseline) to 15 parts per million. Cotinine, a metabolite and biomarker of nicotine, significantly decreased from 4.2 micrograms/mL (baseline) to 0.2 micrograms/mL. All differences in the above three measurements were statistically significant ($P<0.05$).

In a separate Phase II clinical trial funded by Vector Tobacco, our former licensee, under Investigational New Drug ("IND") Application 69,185, a randomized double-blind, active controlled, parallel group, multi-center Phase II smoking cessation clinical trial was conducted to evaluate the quitting efficacy of Quest® reduced-nicotine cigarettes as a smoking cessation treatment in 346 patients (Becker *et al*. 2008, *Nicotine & Tobacco Research* 10:1139-48). Treatment consisted of smoking three reduced-nicotine cigarette styles (Quest 1®, Quest 2® and Quest 3®) for two (2) weeks each, with nicotine yields per cigarette of 0.6 mg (a low nicotine cigarette made with a blend of regular tobacco and our proprietary VLN tobacco), 0.3 mg (an extra low nicotine cigarette made with a blend of regular tobacco and our proprietary VLN tobacco) and 0.05 mg (a VLN cigarette made with tobacco only from our proprietary VLN tobacco variety) either in combination with nicotine patch therapy (a nicotine replacement therapy or NRT product) or placebo patches.

In this three-arm clinical trial in which patients were treated over a period of sixteen (16) weeks, use of reduced-nicotine cigarettes in combination with nicotine patches was more effective (the difference was statistically significant) in achieving four (4)-week continuous abstinence than use of nicotine patches alone (32.8% vs. 21.9%), and use of reduced-nicotine cigarettes without nicotine patches yielded an abstinence rate similar (the difference was not statistically significant) to that of nicotine patches (16.4% vs. 21.9%). No serious adverse events were attributable to the investigational product.

The major differences between the Vector Tobacco Phase II clinical trial and the University of Minnesota Phase II clinical trial is the duration of time during treatment that VLN cigarettes are smoked and the use of nicotine replacement therapy ("NRT') in combination with VLN cigarettes. In the Vector Tobacco trial, VLN cigarettes were smoked by patients (in two arms of the study) for only two (2) weeks, either in combination with using a nicotine patch or placebo patch, followed by continued use of nicotine patches for the subsequent ten (10) weeks. In the University of Minnesota Phase II clinical trial, VLN cigarettes (in one arm of the study) were smoked for six (6) weeks without any use of NRT before, during or after this 6-week treatment period. We believe that the effectiveness of VLN cigarettes for use in smoking cessation is higher when they are used alone (without NRT or another therapy) and for a longer time period, as in the University of Minnesota trial.

A 2008 binding arbitration award, which was completely fulfilled in 2009 by our former licensee, Vector Tobacco, provided us with copies of all of Vector Tobacco's FDA submissions relating to Vector Tobacco's IND for Quest® and awarded to us a right of reference to Vector Tobacco's IND for Quest®, including all results of Vector's Phase II clinical trial. This arbitration award allows us to use all such information in our IND with the FDA for our VLN cigarette that contains our same proprietary tobacco that Vector Tobacco used in its IND submissions to the FDA. This arbitration award has been helpful to us with the FDA, since analytical reports produced by Vector Tobacco pertaining to our proprietary tobacco and cigarettes made from our proprietary tobacco are being utilized by us with the FDA.

A randomized controlled smoking cessation clinical trial using VLN cigarettes was a conducted at Roswell Park Cancer Institute, Buffalo, New York, to investigate the effect of smoking a very low nicotine cigarette ("VLN") in combination with a nicotine patch for 2 weeks prior to the quit date (Rezaishiraz *et al.* 2007 *Nicotine & Tobacco Research* 9:1139-1146). Ninety-eight adult smokers were randomized to two treatments: (i) two (2) weeks of a VLN (Quest 3®) and 21-mg nicotine patch before the quit date and (ii) a reduced nicotine cigarette (Quest 1®) during the two (2) weeks before the quit date. After the quit date, all subjects received counseling for smoking cessation and nicotine patch therapy for up to eight (8) weeks (four (4) weeks of 21-mg patches, two (2) weeks of 14-mg patches, and two (2) weeks of 7-mg patches). Group 1, which used the VLN cigarette and a nicotine patch before quitting, had lower combined craving scores during the two (2) weeks before and after the quit date. Self-reported point prevalence of smoking abstinence at the three (3)- and six (6)-month follow-up points was higher in Group 1 (43% vs. 34% and 28% vs. 21%).

A Phase III/IV two-arm smoking-cessation clinical trial of 1,410 treatment-seeking smokers was conducted by the University of Auckland, Clinical Trials Research Unit (Walker *et al*. 2012 *Addiction* 107: 857–1867)). The 705 patients who received VLN cigarettes in addition to NRT (patches and/or gum or lozenges) had significantly higher cessation rates at all measured time points (3 weeks, 6 weeks, 3 months and 6 months) than patients treated only with NRT. For those who failed to quit, the median time to relapse was increased to two months in the VLN + NRT group, compared to 13 days in the NRT only group. There was no difference in the frequency of serious adverse events between the groups.

A study at Dalhousie University, Halifax, Nova Scotia (Barrett 2010 *Behavioural Pharmacology* 21:144-52), compared the effects of low nicotine cigarettes and an FDA-approved nicotine inhaler on cravings and smoking behavior of smokers who did not intend to quit. In separate laboratory sessions, each of twenty-two (22) participants used a VLN cigarette (Quest 3®), a reduced nicotine cigarette (Quest 1®, which contains approximately two-thirds conventional tobacco and one-third VLN tobacco), a nicotine inhaler (10 mg; 4 mg deliverable, Pharmacia), or a placebo inhaler (identical in appearance to the nicotine inhaler, but containing no nicotine). Cravings, withdrawal and mood descriptors were rated before and after a twenty (20)-minute treatment session during which subjects were instructed to smoke two cigarettes or to use an inhaler every 10 seconds. The reduction in the rating of intent to smoke (usual cigarette brand) after using the VLN cigarette (-10.0) was significantly greater than the reduction with the nicotine inhaler (-1.9). Use of the VLN cigarette was also associated with significantly increased satisfaction and relaxation compared to the nicotine inhaler.

Technology Platform

Our proprietary technology enables us to decrease or increase the level of nicotine (and other nicotinic alkaloids such as nornicotine, anatabine and anabasine) in tobacco plants by decreasing or increasing the expression of gene(s) responsible for nicotine production in the tobacco plant using genetic engineering. The basic techniques, include but are not limited to those that are used in the production of genetically modified (GM) varieties of other crops. However, our proprietary technology can also be implemented without the resulting plants being GM, as long as no foreign DNA not inherent to a plant species such as *Nicotiana tabacum* is present in the engineered plant. In 2009 GM crops were planted on 330 million acres in 25 countries according to the International Service for the Acquisition of Agri-Biotech Applications. This includes approximately 85% of the corn and soybeans grown in the United States. The only components of the technology that are distinct from those in commercialized genetically modified varieties of major crops are segments of tobacco genes (DNA sequences) that are also present in all conventional tobacco plants. Genetically modified or transgenic tobacco that we use in our products has been deregulated by the USDA. Thus, plants may be grown and used in products in the United States without legal restrictions or labeling requirements related to the genetic modification. Nevertheless, our proprietary tobacco is grown only by farmers under contracts that require segregation and prohibit transfer of material to other parties.

During the development of genetically-engineered plant varieties, many candidate plant lines are evaluated in the field in multiple locations over several years, as in any other variety development program. This is carried out in order to identify lines that have not only the specific desired trait, e.g., very low nicotine, but have overall characteristics that are suitable for commercial production of the desired product. This process allows us to see if there are undesirable effects of the genetic modification approach or the specific genetic modification event, regardless of whether the effects are anticipated or unanticipated. For example, since nicotine is known to be an insecticide that is effective against a wide range of insects, reduction of nicotine content in the plants may be expected to affect susceptibility to insect pests. While there are differences in the susceptibility of VLN tobacco to some insects, all tobacco is attacked by a number of insects. The measures taken to control insect pests of conventional tobacco are adequate to control insect pests in VLN tobacco.

Once a genetically-engineered tobacco plant with the desired characteristics is obtained, each plant can produce hundreds of thousands of seeds. When each seed is germinated, the resulting tobacco plant has characteristics similar to the parent and sibling plants and the nicotine content of these plants generally fall within a narrow range. Tobacco products with either low or high nicotine content are easily produced through this method. For example, one of our proprietary tobacco varieties contains the lowest nicotine content of any tobacco ever commercialized, with approximately 95% less nicotine than tobacco in leading “light” cigarette brands. This proprietary tobacco grows with virtually no nicotine without adversely affecting the other leaf constituents important to a cigarette’s characteristics, including taste and aroma.

Sources of Raw Materials

We obtain a large portion of our tobacco leaf requirements from farmers in multiple U.S. states that are under direct contracts with us. The contracts prohibit the transfer of our proprietary seeds and plant materials to other parties. We purchase the balance of our tobacco requirements through third parties. As we expand our sales and distribution of our current commercial brands, *RED SUN* and *MAGIC*, and proceed to market with our *X-22* smoking cessation aid and *BRAND A* and *BRAND B* cigarettes, we plan to continue to scale up the amount of tobacco leaf we obtain directly from farmers under contract.

Intellectual Property

Our proprietary technology is covered by 12 patent families consisting of 107 issued patents in 78 countries, (of these, we own 12 issued patents and we license 95 issued patents on an exclusive basis) and 39 pending patent applications (of these we own 22 patent applications and we license 17 patent applications on an exclusive basis). A “patent family” is a set of patents granted in various countries to protect a single invention. Our patent coverage in the United States and China, the two most valuable smoking cessation and cigarette markets in the word, consists of 15 issued patents and 9 pending applications and 6 issued patents and 3 pending patent applications, respectively. We have exclusive worldwide rights to all uses of the following genes responsible for nicotine content in tobacco plants: QPT, A622,

NBB1, MPO and genes for several transcription factors. We have exclusive rights to plants with altered nicotine content produced from modifying expression of these genes and tobacco products produced from these plants. We also have the exclusive right to license and sublicense these patent rights. The patents owned by or exclusively licensed to us are issued in countries where at least 75% of the world's smokers reside.

We own various registered trademarks in the United States. We also have exclusive rights to plant variety protection, or PVP, certificates in the United States (issued by the U.S. Department of Agriculture) and Canada. A PVP certificate prevents anyone other than the owner/licensee from planting, propagating, selling, importing and exporting a plant variety for twenty (20) years in the U.S. and generally for (20) years in other member countries of the International Union for the Protection of New Varieties of Plants, known as UPOV, an international treaty concerning plant breeders' rights. There are currently more than 70 countries that are members of UPOV.

Sales and Marketing

X-22 Smoking Cessation Aid

We are currently in the process of identifying potential joint venture partners to fund the remaining *X-22* clinical trials. If the FDA approves *X-22* as a smoking cessation aid, Hercules Pharmaceuticals, our subsidiary, intends to enter into arrangements in both the U.S. and international markets with pharmaceutical companies to market and sell *X-22*. We plan to seek marketing partners in the U.S. with existing pharmaceutical sales forces that already call on medical and dental offices in their geographic markets.

There are approximately 700,000 physicians in the U.S., including approximately 80,000 general practitioners, many of whom are aware of new medications, even before they achieve FDA approval. There are also approximately 170,000 dentists in the U.S. who can write prescriptions for smoking cessation aids. Upon FDA approval, we plan to develop awareness for *X-22* by educating physicians and dentists about our *X-22* smoking cessation aid. We intend to advertise in professional journals, use direct mail campaigns to medical professionals, and attend trade shows and professional conferences. We also intend to use internet advertising and pharmacy circulars to reach consumers and to encourage them to ask their physicians and dentists about our *X-22* smoking cessation aid. We expect to use public relations to increase public awareness about *X-22*. We will seek to use federal and state-funded smoking cessation programs and clinics to inform clinicians and patients about, and encourage the use of, *X-22* as a smoking cessation aid. We will also seek to participate in various government-funded programs which purchase approved smoking cessation aids and then distribute these to smokers at no charge or at greatly reduced prices.

RED SUN and MAGIC Cigarettes

Our subsidiary, Goodrich Tobacco, introduced two super-premium priced cigarette brands, *RED SUN* and *MAGIC*, into the U.S. market in the first quarter 2011. Both brands are available in regular and menthol and all brand styles are king size and packaged in hinge-lid hard packs. In the second quarter of 2013, we intend to focus our marketing efforts on tobacconists, smoke shops and tobacco outlets in the U.S. The ban in 2009 by the FDA of all cigarettes with characterizing flavors (with the exception of menthol) has resulted in a product void in these tobacco channels for super-premium priced products. We believe that certain U.S. cigarette wholesalers and retailers will carry our brands, among other reasons, to increase their margins. To facilitate Goodrich Tobacco becoming a participating manufacturer of the “Master Settlement Agreement” or “MSA,” a settlement among 46 states and the tobacco industry administered by the National Association of Attorneys General (“NAAG”), we have curtailed the sales and marketing of these products, especially in 2012. For example, the more *RED SUN* and *MAGIC* that was sold while it was produced by a non-participating manufacturer, the greater settlement cost Goodrich Tobacco likely has to pay to become a participating manufacturer of the MSA.

SPECTRUM Government Research Cigarettes

The National Institute on Drug Abuse (“NIDA”), a component of the National Institutes of Health (“NIH”), provides the scientific community with controlled and uncontrolled research chemicals and drug compounds in its Drug Supply Program. In 2009, NIDA included an option to develop and produce research cigarettes with various levels of nicotine (from very low to high), or Research Cigarette Option, in its request for proposals for a five-year contract for Preparation and Distribution of Research and Drug Products. We have agreed, as a subcontractor to RTI International (“RTI”) in RTI’s contract with NIDA for the Research Cigarette Option, to supply modified nicotine (from very low to high) cigarettes to NIDA. In August 2010, we met with officials from NIDA, FDA, RTI, the National Cancer Institute and the Centers for Disease Control and Prevention to finalize certain aspects of the design of these research cigarettes. These government research cigarettes are distributed under the mark *SPECTRUM*.

BRAND A and BRAND B

The Tobacco Control Act establishes procedures for the FDA to regulate the labeling and marketing of modified risk tobacco products, which includes cigarettes that (i) reduce exposure to tobacco toxins and (ii) are reasonably likely to pose lower health risks as compared to conventional cigarettes ("Modified Risk Cigarettes"). The Tobacco Control Act requires the FDA to issue specific regulations or guidance regarding applications that must be submitted to the FDA for the authorization to label and market Modified Risk Cigarettes. On March 30, 2012, the FDA issued *Modified Risk Tobacco Product Applications Draft Guidance.* We believe that two of our cigarette products, which we refer to as *BRAND A* and *BRAND B*, will qualify as Modified Risk Cigarettes. Compared to commercial cigarettes, the tobacco in *BRAND A* has approximately 95% less nicotine than tobacco in cigarettes previously marketed as "light" cigarettes, and *BRAND B*'s smoke contains an extraordinary low amount of "tar" per milligram of nicotine.

Healthcare Reimbursement

The Affordable Care Act enacted on March 23, 2010 and other government and private sector initiatives targeted to limit the growth of healthcare costs are continuing in the U.S. and many other countries where we intend to sell our *X-22* smoking cessation aid. These changes are causing the marketplace to put increased emphasis on the delivery of more cost-effective medical products.

Government healthcare programs in the United States, including Medicare and Medicaid, private healthcare insurance and managed-care plans have attempted to control costs by limiting the amount of reimbursement for which they will pay for particular procedures or treatments. This may create price sensitivity among potential customers for our *X-22* smoking cessation aid, even if we obtain FDA approval for it. Some third-party payers must also approve coverage for new or innovative devices or therapies before they will reimburse healthcare providers who use the medical devices or therapies. Even though a new medical product may have been cleared for commercial distribution, we may find limited demand for *X-22* until reimbursement approval has been obtained from governmental and private third-party payers.

Approximately 160 million Americans have private health insurance with prescription coverage and the majority, and an increasing number of these plans, cover pharmacologic treatments for smoking cessation. Healthcare payers, including governmental bodies, are increasingly willing to fund smoking cessation treatments due to the expected savings from reducing the incidence of smoking-related illnesses. Approximately 46 million Americans were covered by Medicare in 2009. Medicare provides insurance coverage for up to two smoking cessation attempts per year and each attempt may include four counseling sessions.

Approximately 47 million Americans were covered by state Medicaid programs in 2009. Approximately 30% of Medicaid recipients are smokers. Medicaid programs in 42 states and the District of Columbia cover at least one form of pharmacologic treatment for smoking cessation (Chantix®, Zyban® or NRT). The Affordable Care Act expands Medicaid coverage to all 50 states in 2014. The current retail price of the 12-week prescription of Chantix® is over $450, which should give us great latitude in pricing *X-22*. We expect *X-22* to be price competitive with any FDA-approved smoking cessation aid, especially Chantix®, which will not only encourage governmental and private third-party payers to cover *X-22*, but will encourage smokers to attempt to quit with *X-22* since they will not have to purchase their usual brand of cigarettes over the 6-week treatment period.

Manufacturing

Goodrich Tobacco has thus far had its cigarette brands contract manufactured by a non-participating manufacturer to the MSA. After attempting throughout 2012 to negotiate a contract manufacturing agreement with multiple participating manufacturers to the MSA to have *RED SUN* and *MAGIC* produced by a participating manufacturer to the MSA, and not coming to terms, on January 23, 2013, Goodrich Tobacco applied to the Alcohol and Tobacco Tax Trade Bureau (“TTB”) for a federal permit to manufacture its own tobacco products. Being a federally licensed tobacco product manufacturer is a primary requirement of becoming a participating manufacturer of the MSA. On February 26, 2013, Goodrich Tobacco applied to the NAAG to become a participating manufacturer to the MSA. Both of these measures, if approved by the TTB and NAAG, will greatly facilitate the sales and distribution potential of *RED SUN* and *MAGIC*. To facilitate Goodrich Tobacco becoming a participating manufacturer of the MSA, we have curtailed the sales and marketing of these products, especially in 2012 because the more *RED SUN* and *MAGIC* that is sold while being produced by a non-participating manufacturer, the greater settlement cost Goodrich Tobacco likely has to pay to become a participating manufacturer of the MSA.

Competition

In the market for FDA-approved smoking cessation aids, our principal competitors include Pfizer Inc., GlaxoSmithKline PLC, Novartis International AG, and Niconovum AB, a subsidiary of Reynolds American Inc. The industry consists of major domestic and international companies, most of which have existing relationships in the markets into which we plan to sell, as well as financial, technical, marketing, sales, manufacturing, scaling capacity, distribution and other resources, and name recognition substantially greater than ours.

Cigarette companies compete primarily on the basis of product quality, brand recognition, brand loyalty, taste, innovation, packaging, service, marketing, advertising, retail shelf space and price. Cigarette sales can be significantly influenced by weak economic conditions, erosion of consumer confidence, competitors' introduction of low-price products or innovative products, higher cigarette taxes, higher absolute prices and larger gaps between price categories, and product regulation that diminishes the ability to differentiate tobacco products. Domestic competitors include Philip Morris USA, Reynolds American Inc., Lorillard Inc., Commonwealth Brands, Inc., Liggett Group LCC, Vector Tobacco Inc., and Star Scientific Inc. International competitors include Philip Morris International, British American Tobacco, Japan Tobacco Inc., Imperial Tobacco Group and regional and local tobacco companies; and, in some instances, government-owned tobacco enterprises such as the China National Tobacco Corporation.

Potential Smoking Cessation Aids

Nicotine Vaccines

Nicotine vaccines are under development in clinical trials. However, they have not yet achieved the efficacy of other FDA-approved smoking cessation therapies. Nicotine itself is not recognized by the body as a foreign compound since the molecule is too small. In order to stimulate the production of antibodies, nicotine must be attached to a carrier to make the vaccine work. Different vaccine development programs use different carriers. Six companies, Cytos Biotechnology AG, Celtic Pharmaceuticals Holdings, Nabi Biopharmaceuticals, L.P. and Independent Pharmaceutica AB, Selecta Biosciences Inc., and Pfizer Inc. have or have had vaccine candidates in clinical trials.

Cytos exclusively licensed its nicotine vaccine candidate to Novartis in 2007 for 35 million Swiss Francs ($30 million) and up to 565 million Swiss Francs ($492 million) in milestone payments and royalties. In October 2009, it was announced that Cytos' nicotine vaccine candidate failed to show efficacy in a Phase II trial.

GlaxoSmithKline Biologicals SA exclusively licensed Nabi's nicotine vaccine candidate, NicVAX®, in an agreement which was approved by Nabi's shareholders in March 2010. Together with an upfront non-refundable fee of $40 million paid by GlaxoSmithKline, Nabi is eligible to receive over $500 million in option fees and milestones, not including potential royalties on global sales. Both of Nabi's Phase III NicVAX® clinical trials subsequently failed in 2010 and 2012.

Selecta Biosciences initiated Phase 1 trials of a nicotine vaccine in 2011. Pfizer initiated Phase 1 trials of a nicotine vaccine in 2012.

These vaccine treatments entail six (6) to seven (7) consecutive monthly injections. Increases in abstinence rates have been reported but only among a minority of trial subjects with the highest levels of anti-nicotine antibodies. To date, not all subjects develop sufficient antibody levels despite receiving multiple injections. Even in those who do develop sufficient antibody levels, cravings for cigarettes are not addressed by this treatment, although the pharmacological reward of nicotine is suppressed. Expectations are that the treatment, if approved, would need to be repeated every 12 to 18 months to assist in preventing relapse.

Electronic or E-cigarettes

Although the FDA has not evaluated electronic cigarettes, or e-cigarettes, for quitting smoking, and we are not aware of any published result of a controlled clinical trial of e-cigarettes as a smoking cessation aid comparing efficacy to a placebo or approved therapeutic, e-cigarettes are included here since there have been unconfirmed claims that these products facilitate cessation. E-cigarettes have been the subject of much controversy for this and various other reasons, including the fact that these products are actually not cigarettes at all but are battery-operated devices filled with nicotine, flavor and other chemicals. They turn nicotine and other chemicals into a vapor that is inhaled. E-cigarettes have nicotine kinetics and delivery very similar to nicotine inhalers, a prescription NRT product already approved by the FDA, which is the reason we believe that using e-cigarettes to quit smoking is not likely to be any more effective than other nicotine replacement products.

In a September 9, 2010 press release, the FDA issued warning letters to five e-cigarette distributors for various violations of the Federal Food, Drug, and Cosmetic Act, including unsubstantiated claims and poor manufacturing practices. The FDA said these e-cigarette companies are illegally marketing their products as tools to help people quit using cigarettes. The FDA believes e-cigarettes "[m]eet the definition of a combination drug-device product under the

Federal Food, Drug and Cosmetic Act." In a letter to the Electronic Cigarette Association of the same date, the FDA said the agency intends to regulate electronic cigarettes and related products in a manner consistent with its mission of protecting the public health. Although the number of adverse event reports for tobacco products submitted to the FDA is low, according to the Center for Tobacco Products more than half (46 of 84) of all reports submitted from 2009 through the first quarter of 2012 were for e-cigarettes (Chen, Nicotine Tob Res 15:615-6, 2013).

The FDA confiscated imports of e-cigarettes and has been in litigation with importers of these products. A federal appeals court ruled on December 7, 2010 that the FDA can only regulate electronic cigarettes as tobacco products rather than as a drug-delivery device. The FDA appealed this decision; however, the U.S. Court of Appeals for the District of Columbia Circuit on January 2011 rejected the FDA's request to have the court review the December 7, 2010 decision. According to the FDA Public Health Focus web page on e-cigarettes, the Center for Tobacco Products intends to regulate electronic cigarette products that do not make a therapeutic claim as tobacco products. The Department of Health and Humans Services regulatory calendar for 2013 states that the FDA intends to issue a proposed rule deeming products other than cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco that meet the statutory definition of "tobacco product" to be subject to the Federal Food, Drug, and Cosmetic Act by April 2013. Any e-cigarette product marketed as a smoking cessation aid would still be regulated as a drug-device product by the Center for Drug Evaluation and Research, and efficacy and safety must be evaluated in controlled clinical trials.

Government Regulation

Smoking Cessation Aids

Government authorities in the U.S. and foreign countries extensively regulate the research, development, testing, manufacture, labeling, promotion, advertising, distribution, sampling, marketing and import and export of pharmaceutical products. FDA approval must be obtained, as has been the case for decades, before a product can be marketed for quitting smoking or reducing withdrawal symptoms. In addition, as with all FDA-approved prescription drugs, the FDA must approve the brand name of our *X-22* smoking cessation aid. The FDA approval process for smoking cessation aids is similar to that required by the FDA for new drug approvals, although the cost to complete clinical trials for a smoking cessation aid such as *X-22* are generally far less than clinical trials for drugs. The primary endpoint of the clinical trial for smoking cessation aids is smoking abstinence, which is generally confirmed by inexpensive, noninvasive biomarker tests. Since potential quitters are already smokers, *X-22* will not expose participants in the clinical trials to any new compounds, unlike a new chemical entity, such as Chantix®.

The process of obtaining governmental approvals and complying with ongoing regulatory requirements requires the expenditure of substantial time and financial resources. In addition, statutes, rules, regulations and policies may change and new legislation or regulations may be issued that could delay such approvals. If we fail to comply with applicable regulatory requirements at any time during the product development process, approval process, or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, withdrawals of approvals, clinical holds, warning letters, product recalls, product seizures, total or partial suspension of our operations, injunctions, fines, civil penalties or criminal prosecution. Any agency enforcement action could have a material adverse effect on us.

The U.S. regulatory scheme for the development and commercialization of new drugs can be divided into three distinct phases: an investigational phase including both preclinical and clinical investigations leading up to the submission of a New Drug Application ("NDA"); a period of FDA review culminating in the approval or refusal to approve the NDA; and the post-marketing period.

Preclinical Phase

The preclinical phase involves the characterization, product formulation and animal testing necessary to prepare an IND Application for submission to the FDA. The IND must be reviewed and authorized by the FDA before the drug can be tested in humans. Once a new drug agent has been identified and selected for further development, preclinical testing is conducted to confirm pharmacological activity, to generate safety data, to evaluate prototype dosage forms for appropriate release and activity characteristics, and to confirm the integrity and quality of the material to be used

in clinical trials. A bulk supply of the active ingredient to support the necessary dosing in initial clinical trials must be secured. Data from the preclinical investigations and detailed information on proposed clinical investigations are compiled in an IND submission and submitted to the FDA before human clinical trials may begin. If the FDA does not formally communicate an objection to the IND within 30 days, the specific clinical trials outlined in the IND may go forward.

Clinical Phase

The clinical phase of drug development follows an IND submission and involves the activities necessary to demonstrate the safety, tolerability, efficacy, and dosage of the substance in humans, as well as the ability to produce the substance in accordance with the FDA's cGMP requirements. Data from these activities are compiled in an NDA requesting approval to market the drug for a given use, or indication. Clinical trials must be conducted under the supervision of qualified investigators in accordance with good clinical practice, and according to IND-approved protocols detailing, among other things, the study objectives and the parameters, or endpoints, to be used in assessing safety and efficacy. Each trial must be reviewed, approved and conducted under the auspices of an independent Institutional Review Board ("IRB"), and each trial, with limited exceptions, must include all subjects' informed consent. The clinical evaluation phase typically involves the following sequential process:

Phase I clinical trials are conducted in a limited number of healthy subjects to determine the drug's safety, tolerability, and biological performance. The total number of subjects in Phase I clinical trials varies, but is generally in the range of 20 to 80 people (or less in some cases, such as drugs with significant human experience).

Phase II clinical trials involve administering the drug to subjects suffering from the target disease or condition to evaluate the drug's potential efficacy and appropriate dose. The number of subjects in Phase II trials is typically several hundred subjects or less.

Phase III clinical trials are performed after preliminary evidence suggesting effectiveness has been obtained and safety, tolerability, and appropriate dosing have been established. Phase III clinical trials are intended to gather additional data needed to evaluate the overall benefit-risk relationship of the drug and to provide adequate instructions for its use. Phase III trials usually include several hundred to several thousand subjects.

Throughout the clinical testing phase, samples of the product made in different batches are tested for stability to establish shelf life constraints. In addition, increasingly large-scale production protocols and written standard operating procedures must be developed for each aspect of commercial manufacturing and testing.

The clinical trial phase is both costly and time-consuming, and may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted under an IND and may, at its discretion, reevaluate, alter, suspend, or terminate the testing at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request additional clinical testing as a condition to product approval. Additionally, new government requirements may be established that could delay or prevent regulatory approval of our products under development. Furthermore, institutional review boards, which are independent entities constituted to protect human subjects in the institutions in which clinical trials are being conducted, have the authority to suspend clinical trials in their respective institutions at any time for a variety of reasons, including safety issues.

New Drug Application and Review

After the completion of Phase III clinical trials, the sponsor of the new drug submits an NDA to the FDA requesting approval to market the product for one or more indications. An NDA is a comprehensive, multi-volume application that includes, among other things, the results of all preclinical and clinical studies, information about the drug's composition, and the sponsor's plans for producing, packaging, and labeling the drug. In most cases, the NDA must be accompanied by a substantial user fee. The FDA has 60 days after submission to review the completeness and organization of the application, and may refuse to accept it for continued review, or refuse to file, if the application is found deficient. After filing, the FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use. Drugs that successfully complete NDA review may be marketed in the United States, subject to all conditions imposed by the FDA.

Prior to granting approval, the FDA generally conducts an inspection of the facilities, including outsourced facilities that will be involved in the manufacture, production, packaging, testing and control of the drug for cGMP compliance. The FDA will not approve the application unless cGMP compliance is satisfactory. If the FDA determines that the marketing application, manufacturing process, or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and will often request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the marketing application does not satisfy the regulatory criteria for approval and refuse to approve the application by issuing a "not approvable" letter.

The length of the FDA's review can range from a few months to several years or more. Once an NDA is in effect, significant changes such as the addition of one or more new indications for use generally require prior approval of a supplemental NDA including additional clinical trials or other data required to demonstrate that the product as

modified remains safe and effective.

Fast Track Development

The Food and Drug Administration Modernization Act of 1997 (the "Modernization Act"), establishes a statutory program for relatively streamlined approval of "Fast Track" products, which are defined under the Modernization Act as new drugs or biologics intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for this condition. Fast Track status requires an official designation by the FDA. The Tobacco Control Act provides that products for smoking cessation, such as *X-22*, be considered for "Fast Track" designation by the FDA.

A product that receives Fast Track designation is eligible for (i) more frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, and (ii) more frequent written correspondence from the FDA about such things as the design of the proposed clinical trials. A Fast Track product is also eligible for Rolling Review, in which sections of the NDA can be submitted for review by the FDA before the entire application is completed. A Fast Track product would ordinarily meet FDA criteria for Priority Review. The FDA goal for reviewing a drug with Priority Review status is six months from the filing of the NDA.

We submitted a request for Fast Track designation for *X-22*, and on August 18, 2011, the FDA informed us that it would not grant the designation of *X-22* as a Fast Track product at that time because we did not demonstrate that X-22 shows potential to address an unmet medical need. Except for our Phase II-B clinical trial, all smoking cessation studies with very low nicotine ("VLN") cigarettes containing our proprietary tobacco were independent studies and were not sponsored by 22nd Century Ltd under its own Investigational New Drug ("IND"). We plan to reapply for Fast Track designation, but not until results of a clinical trial conducted by us demonstrates an advantage (over currently approved smoking cessation products) in one of the following areas: efficacy, safety or improvement in some other factor such as compliance (a patient using a product as directed) or convenience. There is no guarantee that the FDA will grant Fast Track designation to *X-22*.

Post-Approval Phase

Once the FDA has approved a new drug for marketing, the product becomes available for physicians to prescribe in the U.S. After approval, we must comply with post-approval requirements, including ongoing compliance with cGMP regulations, delivering periodic reports to the FDA, submitting descriptions of any adverse reactions reported, and complying with drug sampling and distribution requirements. We are required to maintain and provide updated safety and efficacy information to the FDA. We must also comply with requirements concerning advertising, product promotions, and labeling.

Company Sponsored X-22 Clinical Trials

We have met with the FDA regarding the remaining *X-22* clinical trials and, based on the FDA's guidance, we developed a plan to conduct a small Phase II-B trial and two larger and concurrent Phase III trials with the same protocols that entail measuring the quitting efficacy of the *X-22* cigarette against a typical cigarette with conventional nicotine content that is visually indistinguishable from *X-22* (the "active control"). Half of the participants smoke *X-22* for six (6) weeks and half of the participants will smoke the active control for six (6) weeks, with all participants instructed to quit on the last day of the six (6)-week treatment period.

Smokers who do not smoke over the four (4)-week period immediately following the conclusion of the six (6)-week treatment period (weeks 7 through 10) are considered abstinent. The abstinence (quit) rates of the *X-22* group and the active control group are compared for statistical significance.

Our Investigational New Drug Application for *X-22*, a kit of VLN cigarettes, was cleared by the FDA in July 2011. Our *X-22* Phase II-B clinical trial was completed in the first quarter of 2012 and did not demonstrate a statistically significant difference in quitting between *X-22* and the active control, a cigarette containing conventional nicotine levels. In evaluating the results of this trial, we believe we may have reduced the nicotine content of *X-22* by too great

a percentage, to a level less than half the nicotine content of VLN cigarettes used in various independent smoking-cessation clinical trials that have demonstrated that use of VLN cigarettes increases quit rates.

We continue to believe that our VLN cigarettes are effective as a smoking cessation aid. However, we have suspended sponsoring further *X-22* clinical trials pending a complete analysis of results of two independent smoking-cessation trials that were completed in 2012 (ClinicalTrials.gov Identifiers NCT01050569 and NCT01250301), which utilized a different version of our VLN cigarette with a nicotine content similar to those used in previous successful smoking-cessation trials and higher than that used in our own sponsored Phase II-B trial. A portion of the results of these two trials has been disclosed at the 2013 annual meeting of the Society for Research on Nicotine and Tobacco. These preliminary results are promising for the further development of *X-22*.

The full set of results of these 2 independent clinical trials are expected to be published in peer reviewed journals and will be compared to results of other independent clinical trials of our VLN cigarettes and results of our Phase II-B trial to determine which variables optimize cessation. One preliminary hypothesis, in conjunction with results of various other studies of our VLN cigarettes, is that having two types of prescription VLN cigarettes available may be advantageous for increased smoking cessation in the general population; one having a higher nicotine content than the other. Upon identifying a suitable joint venture partner to fund further *X-22* clinical trials, we will then request a meeting with the U.S. Food and Drug Administration ("FDA"), and thereafter we may resume our own sponsored *X-22* clinical trials.

Following FDA approval, we intend to register *X-22* as a Medicinal Product (pharmacological) for smoking cessation with the European Medicines Agency ("EMA") and other international FDA-equivalent agencies in targeted countries. Regulatory approval for *X-22* as a smoking cessation aid is not required in some international markets since, unlike the FDA, some foreign drug regulatory agencies do not require approval to market a product as a smoking cessation aid if the product is allowed to be sold for other purposes.

Modified Risk Cigarettes

The Tobacco Control Act, which became law in June 2009, prohibits the FDA from banning cigarettes outright or mandating that nicotine levels be reduced to zero. However, among other things, it allows the FDA to require the reduction of nicotine or any other compound in cigarettes. In 2009, the Tobacco Control Act banned all sales in the United States of cigarettes with flavored tobacco (other than menthol). As of June 2010, all cigarette companies were required to cease using the terms "low tar," "light" and "ultra light" in describing cigarettes sold in the United States. We believe this new regulatory environment represents a paradigm shift for the tobacco industry and will create opportunities for us in marketing *BRAND A* and *BRAND B* and in licensing our proprietary technology and/or tobaccos to larger competitors.

For the first time in history, a U.S. regulatory agency will scientifically evaluate cigarettes that may pose lower health risks as compared to conventional cigarettes. The Tobacco Control Act establishes procedures for the FDA to regulate the labeling and marketing of modified risk tobacco products, which includes cigarettes that (i) reduce exposure to tobacco smoke toxins and/or (ii) pose lower health risks, as compared to conventional cigarettes ("Modified Risk Cigarettes"). The Tobacco Control Act requires the FDA to issue specific regulations and guidance regarding applications that must be submitted to the FDA for the authorization to label and market Modified Risk Cigarettes. We believe that *BRAND A* and *BRAND B* will qualify as Modified Risk Cigarettes. We will need significant additional capital to complete the FDA authorization process for our Modified Risk Cigarettes. The amount of capital is currently unknown since it is uncertain how many exposure studies the FDA will require for *BRAND A* and *BRAND B*. In addition, the Tobacco Control Act allows the FDA to mandate the use of reduced risk technologies in conventional tobacco products and cigarettes (e.g., Marlboro®) which could create opportunities for us to license our proprietary technology and/or our tobaccos to larger competitors.

In addition to providing our *SPECTRUM* cigarettes to NIDA for researchers, we have been directly supplying our cigarettes to researchers so additional studies can be conducted to obtain additional information on our products. We expect this information will assist us, along with our own funded studies, in obtaining the necessary FDA authorizations to market *BRAND A* and *BRAND B* as Modified Risk Cigarettes and to obtain FDA approval for *X-22* as a prescription smoking cessation aid.

Biomass Products

Biomass products are products such as ethanol made from the organic material, usually plants densely grown over a given area. We have funded extensive biomass field trials conducted by North Carolina State University ("NCSU"), and work on feedstock digestibility and bioconversion at the National Renewable Energy Lab. Bioconversion is the conversion of organic matter into a source of energy, such as ethanol in our own research, through the action of microorganisms. Tobacco has a number of advantages as a starting point for development of novel bioproduct crop systems. Because tobacco is a widely cultivated crop, grown in over 100 countries throughout the world, tobacco agronomy is highly understood. For decades tobacco has been used as a model system for plant biology, and recently the tobacco genome has been mapped. Tobacco plants rapidly sprout back after each harvest and produce large amounts of leaf and total biomass. Tobacco grown for cigarettes yields about 3,000 pounds of cured leaf per acre (~20% moisture) per year from 7,500 tobacco plants. In our field trials in North Carolina, nicotine-free tobacco grown for biomass yields about 100,000 pounds of fresh weight per acre (which equals 10,000 pounds of dry weight) per year with multiple machine harvests from about 80,000 tobacco plants. The results of our biomass studies have been summarized in a comprehensive feasibility study relating to our nicotine-free tobacco biomass crop (*Verfola*) to produce a variety of bioproducts. First, protein and other plant fractions are extracted, and then biofuels and other products are produced from the remaining cellulosic residue.

In 2008, we put our biomass development projects on hold so that our management could focus its attention and resources on our modified risk cigarette business and our *X-22* smoking cessation business. We do not plan to move forward with potential biomass business activities until some period of time after FDA approval of *X-22* or FDA

authorization to market *Brand A* or *Brand B* as a Modified Risk Cigarette. We currently are not spending any

capital for such potential biomass business activities nor do we have any current plans to raise any capital for such potential biomass business activities.

Research and Development

Most research and development (R&D) since our inception have been outsourced to highly qualified groups in their respective fields. Since 1998, 22nd Century has had multiple R&D agreements with North Carolina State University ("NCSU") resulting in exclusive worldwide licenses to various patented technologies. We have utilized the model of many public-sector research organizations which entails obtaining an exclusive option or license agreement to any invention arising out of the funded research. In all cases, we fund and exclusively control all patent filings as the exclusive licensee. This model of contracting with public-sector researchers has enabled 22nd Century to control R&D costs while achieving our desired results, including obtaining exclusive intellectual property rights relating to all of our outsourced R&D.

Other R&D partners with the same arrangement have included the National Research Council of Canada, Plant Biotechnology Institute in Saskatoon, Canada ("NRC"), and the Nara Institute of Science and Technology in Nara, Japan ("NAIST"). The majority this R&D has involved the biosynthesis of nicotine in plants. Our R&D agreements with NCSU, NRC and NAIST expired in 2009. We did not have any outsourced R&D projects during 2010. In 2010, NAIST assigned to us all of their worldwide patents and patent applications that were previously licensed to 22nd Century on an exclusive basis. These patents and patent applications were a result of our R&D at NAIST. In November 2011, we entered into an R&D agreement with the University of Virginia (UVA) relating to nicotine biosynthesis in tobacco plants with a total budget of $500,000 for the period from November 2011 through December 2014. In 2012, we incurred approximately $100,000 of expenses for the R&D agreement at UVA. During the years ended December 31, 2012, 2011 and 2010, we incurred research and development expenses of approximately $729,000, $2,098,000 and $364,000, respectively.

Other than the R&D agreement at UVA, we have no other substantial third-party R&D commitments requiring funding. However, we may carry out a minimal amount of R&D in 2013, not to exceed $100,000, for additional field trials of plants from our seed lots that resulted from our R&D at NCSU, NRC, NAIST and UVA. Upon the required funding, we expect to carry out exposure studies for our modified risk cigarette candidates and will carry out additional clinical trials for *X-22* if Hercules Pharmaceuticals, our subsidiary, identifies a joint venture partner willing to fund these trials.

Employees

We currently employ six (6) people, none of whom are represented by a union, and we consider our employee relations to be good.

Item 1A. Risk Factors.

Risks Related to Our Business and Operations

We may not be able to continue as a going concern unless we obtain additional capital and future sales of equity securities will cause stockholders to experience substantial dilution.

Recurring losses from operations, our negative working capital of approximately $3.3 million and $1.9 million as of December 31, 2012 and 2011, respectively, shareholders' deficit of $6.1 million and $1.2 million as of December 31, 2012 and 2011, respectively, and the uncertainty of obtaining additional capital on a timely basis, raise doubt about our ability to continue as a going concern. It is highly probable that any sales of equity securities will cause our stockholders to experience substantial dilution. It is also possible that such equity securities will have rights, preferences or privileges senior to those of existing stockholders. The report of our independent registered public accounting firm on our financial statements for the year ended December 31, 2012 expresses substantial doubt regarding whether we can continue as a going concern. We cannot guarantee our ability to continue as a going concern.

We have had a history of losses, and we may be unable to achieve or sustain profitability.

We experienced net losses, including adjustment of our warrant liability, of approximately $6.7 million, $1.3 million and $1.4 million during the years ended December 31, 2012, 2011 and 2010, respectively. We expect to continue to

incur net losses and negative operating cash flows in the foreseeable future and cannot be certain that we will ever achieve profitability. Excluding extraordinary expenses such as clinical trials, our monthly expenses are approximately $125,000. Since 2007, we have received only limited licensing revenue from a former licensee and our only significant revenue has been from research cigarettes for which the market is limited. We will need to spend significant capital to fulfill planned operating goals and conduct clinical studies, achieve regulatory approvals and, subject to such approvals, successfully produce products for commercialization. Excluding contract growing of our proprietary tobacco with farmers and extraordinary expenses such as clinical trials and factory setup costs, our monthly cash expenditures are approximately $100,000. In the event the Company does not enter into an out-licensing agreement with a third party in 2013, approximately $1.6 million of additional cash is required through 2013, which includes paying approximately $1 million of obligations that will become due in 2013. There can be no assurance that the Company will be able to raise sufficient financing or obtain a licensing agreement.

We have a history of negative cash flow, and our ability to generate positive cash flow is uncertain.

We had negative cash flow before financing activities of approximately $1,927,000, $4,057,000 and $1,018,000 during the years ended December 31, 2012, 2011 and 2010, respectively. We anticipate that we will continue to have negative cash flow for the foreseeable future even though we have suspended clinical trials for *X-22* because we have significant liabilities that are due or that will become due in 2013 and we will continue to incur expenses for sales and marketing, and general and administrative expenses. Our business will also require significant amounts of working capital to support our growth. Therefore, we will likely need to raise additional investment capital to achieve growth, and we may not achieve sufficient revenue growth to generate positive future cash flow. An inability to generate positive cash flow for the foreseeable future or raise additional capital on reasonable terms may decrease our long-term viability.

Our ability to obtain future debt financing is limited while shares of our Series A-1 Preferred Stock are outstanding.

Our Certificate of Designations regarding our Series A-1 Preferred Stock contains restrictive covenants that limit our ability to, among other things, incur or assume additional debt or provide guarantees in respect of obligations of other persons (in each case, so long as 1,000 or more shares of our Series A-1 Preferred Stock are outstanding, and other than with respect to lease obligations and purchase money indebtedness in an amount up to $200,000 in the aggregate), or create, assume, or suffer to exist any liens (other than liens for taxes not yet due, liens contested in good faith, and liens imposed in the ordinary course of business that do not materially impair the operation of the business) without, in each instance, the prior written consent of at least 67% in stated value of the then-outstanding shares of Series A-1 Preferred Stock. A breach of these covenants would trigger the ability of the holders of the Series A-1 Preferred Stock to redeem their shares of Series A-1 Preferred Stock for cash or shares of our common stock or elect to increase the dividend payments to be made on their shares of Series A-1 Preferred Stock to 18% per annum. However, our Certificate of Designations regarding our Series A-1 Preferred Stock allows us to issue securities without restrictions pursuant to strategic transactions approved by a majority of our disinterested directors, provided that any such issuance shall only be to an entity which is, itself or through its subsidiaries, an operating company or an owner of an asset in a business synergistic with our business which provides us additional benefits in addition to the investment of funds.

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Our limited operating history makes it difficult to evaluate our current business and future prospects.

We have been in existence since 1998, but our activities have been limited primarily to licensing and funding research and development activities. Our limited operating history may make it difficult to evaluate our current business and our future prospects. We have encountered and will continue to encounter risks and difficulties frequently experienced by growing companies in rapidly changing industries, including increasing expenses as we continue to grow our business. If we do not manage these risks successfully, our business will be harmed.

We have no experience in managing growth. If we fail to manage our growth effectively, we may be unable to execute our business plan or address competitive challenges adequately.

We currently have six employees. Any growth in our business will place a significant strain on our managerial, administrative, operational, financial, information technology and other resources. We intend to further expand our overall business, customer base, employees and operations, which will require substantial management effort and significant additional investment in our infrastructure. We will be required to continue to improve our operational, financial and management controls and our reporting procedures and we may not be able to do so effectively. As such, we may be unable to manage our growth effectively.

Our working capital requirements involve estimates based on demand expectations and may increase beyond those currently anticipated, which could harm our operating results and financial condition.

We have no experience in selling smoking cessation products or Modified Risk Cigarettes on a commercial basis. As a result, we intend to base our funding and inventory decisions on estimates of future demand. If demand for our products does not increase as quickly as we have estimated, our inventory and expenses could rise, and our business and operating results could suffer. Alternatively, if we experience sales in excess of our estimates, our working capital needs may be higher than those currently anticipated. Our ability to meet any demand for our products may depend on our ability to arrange for additional financing for any ongoing working capital shortages, since it is likely that cash flow from sales will lag behind our investment requirements.

We have suspended further clinical trials for FDA approval of our X-22 smoking cessation aid and we will need additional capital before we can complete the FDA authorization process for our Modified Risk Cigarettes.

We have suspended further clinical trials for FDA approval of our *X-22* smoking cessation aid until we identify a suitable joint venture partner willing to fund further *X-22* clinical trials. At that time we may resume our own

sponsored *X-22* clinical trials. There is no guarantee that we will identify a joint venture partner willing to fund further *X-22* clinical trials. We estimate the cost of completing a Phase II trial will be approximately $2 million and the cost of completing two Phase III trials to be approximately $12 million. We will require additional capital in the future before we can complete the FDA authorization process for our Modified Risk Cigarettes. We estimate that the cost of completing the FDA authorization process for each of our two potential Modified Risk Cigarettes to be at least $2 million. If we raise additional funds through the issuance of equity securities for the FDA authorization process for our Modified Risk Cigarettes, our stockholders may experience substantial dilution, or the equity securities may have rights, preferences or privileges senior to those of existing stockholders. If we raise additional funds through debt financings, these financings may involve significant cash payment obligations and covenants that restrict our ability to operate our business and make distributions to our stockholders. However, our ability to raise funds through debt financing is limited while any shares of our Series A-1 Preferred Stock is outstanding. We also could elect to seek funds through arrangements with collaborators or licensees. To the extent that we raise additional funds through collaboration and licensing arrangements, it may be necessary to relinquish some rights to our technologies or our potential products or grant licenses on terms that are not favorable to us.

If we choose to resume our own clinical trials for FDA approval of our *X-22* smoking cessation product and we cannot raise additional capital on acceptable terms, we may not be able to, among other things:

• complete clinical trials of our *X-22* smoking cessation aid;

• undertake the steps necessary to seek FDA authorization of our Modified Risk Cigarettes;

• develop or enhance our potential products or introduce new products;

• expand our development, sales and marketing and general and administrative activities;

• attract tobacco growers, customers or manufacturing and distribution partners;

• acquire complementary technologies, products or businesses;

• expand our operations in the United States or internationally;

• hire, train and retain employees; or

• respond to competitive pressures or unanticipated working capital requirements.

We currently are not in compliance with annual "clean-up" provisions under a revolving line of credit.

Included in current liabilities at December 31, 2012 is a demand loan under a revolving credit agreement with a balance outstanding of $174,925, which is payable to a commercial bank and guaranteed by one of our shareholders. This exact same principal amount has been outstanding for over four years on a continuous basis, notwithstanding the fact that we have not complied with annual "clean-up" provisions which require that we repay all amounts outstanding for a period of 30 consecutive days each year. There are no additional amounts available to us under this credit agreement. We have paid interest only since 2008 (currently at the bank's annual prime rate plus 0.75% or 4%) on a monthly basis according to the bank's monthly payment statements. Our plans contemplate that this balance remains outstanding while we continue to pay interest only on a monthly basis. We may incur disruptions in our operations in the event the bank were to demand repayment in full, close the revolving credit agreement, and not allow us sufficient time to locate additional capital.

We will depend on third parties to manufacture our products.

We currently do not manufacture any of our products and depend on contract manufacturers to produce our products according to our specifications, in sufficient quantities, on time, in compliance with appropriate regulatory standards and at competitive prices. We currently do not have an arrangement with any contract manufacturer to produce our final version of *X-22* smoking cessation aid once it is approved by the FDA.

Manufacturers supplying our potential products must comply with FDA regulations which require, among other things, compliance with the FDA's evolving regulations on Current Good Manufacturing Practices ("cGMP(s)"), which are enforced by the FDA through its facilities inspection program. The manufacture of products at any facility will be subject to strict quality control, testing and record keeping requirements, and continuing obligations regarding the submission of safety reports and other post-market information. We cannot guarantee that our current contract manufacturers will pass FDA and/or similar inspections in foreign countries to produce the final version of our *X-22* smoking cessation aid, or that future changes to cGMP manufacturing standards will not also affect the manufactures of our other products. Therefore, we may have to build our own manufacturing facility which would require additional capital.

We will mainly depend on third parties to market, sell and distribute our products, and we currently have no commercial arrangements for the marketing, sale or distribution of our X-22 smoking cessation aid.

We expect to depend on third parties to a great extent to market, sell and distribute our products and we currently have no arrangements with third parties in place to provide such services for our *X-22* smoking cessation aid. We cannot be sure that we will be able to enter into such arrangements on acceptable terms, or at all.

If we are unable to enter into marketing, sales and distribution arrangements with third parties for our *X-22* smoking cessation aid, we would need to incur significant sales, marketing and distribution expenses in connection with the commercialization of *X-22* and any future potential products. We do not currently have a dedicated sales force, and we have no experience in the sales, marketing and distribution of pharmaceutical products. Developing a sales force is expensive and time-consuming, and we may not be able to develop this capacity. If we are unable to establish adequate sales, marketing and distribution capabilities, independently or with others, we may not be able to generate significant revenue and may not become profitable.

If our X-22 smoking cessation aid does not gain market acceptance among physicians, patients, third-party payers and the medical community, we may be unable to generate significant revenue.

Our *X-22* smoking cessation aid may not achieve market acceptance among physicians, patients, third-party payers and others in the medical community. If we receive FDA approval for the marketing of *X-22* as a smoking cessation aid in the U.S., the degree of market acceptance could depend upon a number of factors, including:

- limitations on the indications for use for which *X-22* may be marketed;
- the establishment and demonstration in the medical community of the clinical efficacy and safety of our potential products and their potential advantages over existing products;
- the prevalence and severity of any side effects;
- the strength of marketing and distribution support; and
- sufficient third-party coverage or reimbursement.

The market may not accept our *X-22* smoking cessation aid, based on any number of the above factors. Even if the FDA approves the marketing of *X-22* as a smoking cessation aid, there are other FDA-approved products available and there will also be future competitive products which directly compete with *X-22*. The market may prefer such existing or future competitive products for any number of reasons, including familiarity with or pricing of such products. The failure of any of our potential products to gain market acceptance could impair our ability to generate revenue, which could have a material adverse effect on our future business, financial condition, results of operations and cash flows.

Our principal competitors in the smoking cessation market have, and any future competitors may have, greater financial and marketing resources than we do, and they may therefore develop products or other technologies similar or superior to ours or otherwise compete more successfully than we do.

We have no experience in selling smoking cessation products. Competition in the smoking cessation aid products industry is intense, and we may not be able to successfully compete in the market. In the market for FDA-approved smoking cessation aids, our principal competitors include Pfizer Inc., GlaxoSmithKline PLC, Perrigo Company, Novartis International AG, and Niconovum AB, a subsidiary of Reynolds American Inc. The industry consists of major domestic and international companies, most of which have existing relationships in the markets which we plan to sell, as well as financial, technical, marketing, sales, manufacturing, scaling capacity, distribution and other resources and name recognition substantially greater than ours. In addition, we expect new competitors will enter the markets for our products in the future. Potential customers may choose to do business with our more established competitors, because of their perception that our competitors are more stable, are more likely to complete various projects, can scale operations more quickly, have greater manufacturing capacity, are more likely to continue as a going concern and lend greater credibility to any joint venture. If we are unable to compete successfully against manufacturers of other smoking cessation products, our business could suffer, and we could lose or be unable to obtain market share.

We face intense competition in the market for our RED SUN and MAGIC cigarettes and our BRAND A and BRAND B cigarettes, and our failure to compete effectively could have a material adverse effect on our profitability and results of operations.

Cigarette companies compete primarily on the basis of product quality, brand recognition, brand loyalty, taste, innovation, packaging, service, marketing, advertising, retail shelf space and price. We are subject to highly competitive conditions in all aspects of our business and we may not be able to effectively market and sell our *RED SUN and MAGIC* cigarettes or other cigarettes we may introduce to the market such as our *BRAND A* and *BRAND B* cigarettes as Modified Risk Cigarettes, upon FDA authorization. The competitive environment and our competitive position can be significantly influenced by weak economic conditions, erosion of consumer confidence, competitors' introduction of low-price products or innovative products, higher cigarette taxes, higher absolute prices and larger gaps between price categories, and product regulation that diminishes the ability to differentiate tobacco products. Domestic competitors include Philip Morris USA Inc., Reynolds American Inc., Lorillard Inc., Commonwealth Brands, Inc., Liggett Group LLC, Vector Tobacco Inc. and Star Scientific Inc. International competitors include Philip

Morris International Inc., British American Tobacco, JT International SA, Imperial Tobacco Group PLC and regional and local tobacco companies; and in some instances, government-owned tobacco enterprises such as the China National Tobacco Corporation.

Our competitors may develop products that are less expensive, safer or more effective, which may diminish or eliminate the commercial success of any potential product that we may commercialize.

If our competitors market products that are less expensive, safer or more effective than our potential products, or that reach the market before our potential products, we may not achieve commercial success. The market may choose to continue utilizing existing products for any number of reasons, including familiarity with or pricing of these existing products. The failure of our *X*-22 smoking cessation aid or our cigarette brands to compete with products marketed by our competitors would impair our ability to generate revenue, which would have a material adverse effect on our future business, financial condition, results of operations and cash flows. Our competitors may:

• develop and market products that are less expensive or more effective than our products;

• commercialize competing products before we or our partners can launch our products; and

• initiate or withstand substantial price competition more successfully than we can.

If we fail to stay at the forefront of technological change, we may be unable to compete effectively.

Our competitors may render our technologies obsolete by advances in existing technological approaches or the development of new or different approaches, potentially eliminating the advantages that we believe we derive from our research approach and proprietary technologies. Our competitors may:

• operate larger research and development programs or have substantially greater financial resources than we do;

• have greater success in recruiting skilled technical and scientific workers from the limited pool of available talent;

• more effectively negotiate third-party licenses and strategic relationships; and

• take advantage of acquisition or other opportunities more readily than we can.

Government mandated prices, production control programs, shifts in crops driven by economic conditions and adverse weather patterns may increase the cost or reduce the quality of the tobacco and other agricultural products used to manufacture our products.

We depend upon independent tobacco farmers to grow our specialty proprietary tobaccos with specific nicotine contents for our products. As with other agricultural commodities, the price of tobacco leaf can be influenced by imbalances in supply and demand, and crop quality can be influenced by variations in weather patterns, diseases and pests. We must also compete with other tobacco companies for contract production with independent tobacco farmers. Tobacco production in certain countries is subject to a variety of controls, including government mandated prices and production control programs. Changes in the patterns of demand for agricultural products could cause farmers to plant less tobacco. Any significant change in tobacco leaf prices, quality and quantity could affect our profitability and our business.

Our future success depends on our ability to retain key personnel.

Our success will depend to a significant extent on the continued services of our senior management team, and in particular Joseph Pandolfino, our Chief Executive Officer, Henry Sicignano III, our Chief Financial Officer and President, and Michael Moynihan, Ph.D., our Vice President of R&D. The loss or unavailability of any of these individuals may significantly delay or prevent the development of our potential products and other business objectives by diverting management's attention to transition matters. While each of these individuals is party to employment agreements with us, they could terminate their relationships with us at any time, and we may be unable to enforce any applicable employment or non-compete agreements.

We also rely on consultants and advisors to assist us in formulating our research and development, manufacturing, distribution, marketing and sales strategies. All of our consultants and advisors are either self-employed or employed by other organizations, and they may have conflicts of interest or other commitments, such as consulting or advisory contracts with other organizations, that may affect their ability to contribute to us.

Product liability claims, product recalls or other claims could cause us to incur losses or damage our reputation.

The risk of product liability claims or product recalls, and associated adverse publicity, is inherent in the development, manufacturing, marketing and sale of tobacco and smoking cessation products. We do not currently have product liability insurance for our products or our potential products and do not expect to be able to obtain product liability insurance at reasonable commercial rates for these products. Any product recall or lawsuit seeking significant monetary damages may have a material adverse effect on our business and financial condition. A successful product liability claim against us could require us to pay a substantial monetary award. We cannot assure you that such claims will not be made in the future.

Risks Related to Regulatory Approvals and Insurance Reimbursement

If we fail to obtain FDA and foreign regulatory approvals of X-22 as a smoking cessation aid and FDA authorization to market BRAND A and BRAND B as Modified Risk Cigarettes, we will be unable to commercialize these potential products in and outside the U.S., other than the sale of our BRAND A and BRAND B cigarettes as conventional cigarettes.

There can be no assurance that our *X-22* smoking cessation aid will be approved by the FDA, European Medicines Agency, or any other governmental body. In addition, there can be no assurance that all necessary approvals will be granted for our potential products or that review or actions will not involve delays caused by requests for additional information or testing that could adversely affect the time to market for and sale of our potential products. Our ability to complete the FDA-approval process in a timely manner is dependent, in part, on our ability to obtain “Fast Track” designation for *X-22* by the FDA.

We submitted a request for Fast Track designation for *X-22*, and on August 18, 2011, the FDA informed us that it would not grant the designation of *X-22* as a Fast Track product at this time because we did not demonstrate that *X-22* shows potential to address an unmet medical need. Except for our Phase II-B clinical trial, all smoking cessation studies with very low nicotine ("VLN") cigarettes containing our proprietary tobacco were independent studies and were not sponsored by 22nd Century Ltd under its own Investigational New Drug ("IND"). We plan to reapply for Fast Track designation, but not until results of a clinical trial conducted by us demonstrates an advantage (over currently approved smoking cessation products) in one of the following areas: efficacy, safety or improvement in some other factor such as compliance (a patient using a product as directed) or convenience. There is no guarantee that the FDA will grant Fast Track designation to *X-22*. We may also not obtain Priority Review of our *X-22* New Drug Application (NDA), which would further delay FDA approval of *X-22*. The length of the FDA's review of a New Drug Application without a Priority Review designation is normally ten months from the date of filing of the New Drug Application, although it is possible in certain cases for such review time to be longer. However, the FDA's goal for reviewing a product with Priority Review status is normally six months from the date of the filing of a NDA. If we do not obtain Priority Review of our New Drug Application, we would then expect the timing of FDA approval of *X-22* to be extended several additional months. Even if *X-22* is approved by the FDA, the FDA may require the product to only be prescribed to patients who have already failed to quit smoking with another approved therapy. Further, failure to comply with applicable regulatory requirements can, among other things, result in the suspension of regulatory approval as well as possible civil and criminal sanctions.

The development, testing, manufacturing and marketing of our potential products are subject to extensive regulation by governmental authorities in the United States and throughout the world. In particular, the process of obtaining approvals by the FDA, European Medicines Agency and other international FDA equivalent agencies in targeted countries is costly and time consuming, and the time required for such approval is uncertain. Our *X-22* smoking cessation aid must undergo rigorous clinical testing and an extensive regulatory approval process mandated by the FDA or EMEA. Such regulatory review includes the determination of manufacturing capability and product performance. Generally, only a small percentage of pharmaceutical products are ultimately approved for commercial sale.

The scope of review, including product testing and exposure studies, to be required by the FDA under the Tobacco Control Act in order for cigarettes such as *BRAND A* and *BRAND B* to be marketed as Modified Risk Cigarettes has not yet been fully established. We may be unsuccessful in establishing that *BRAND A* or *BRAND B* are Modified Risk Cigarettes, and we may fail to demonstrate that either *BRAND A* or *BRAND B* significantly reduces exposure to certain tobacco smoke toxins. Even upon demonstrating significant reduced exposure to certain tobacco smoke toxins, the FDA may decide that allowing a modified risk claim is not in the best interest of the public health, and the FDA may not allow us to market our *BRAND A* and/or *BRAND B* cigarettes as Modified Risk Cigarettes. Furthermore, the FDA could force us to remove from the U.S. market our other tobacco products such as *RED SUN* or *MAGIC* and even *BRAND A* and/or *BRAND B* after FDA authorization to market *BRAND A* and *BRAND B* as Modified Risk Cigarettes.

In the future, we intend to distribute and sell our potential products outside of the United States, which will subject us to further regulatory risk.

In addition to seeking approval from the FDA for our *X-22* smoking cessation aid in the United States, we intend to seek governmental approvals required to market *X-22* and our other potential products in other countries. Marketing of our *X-22* smoking cessation aid is not permitted in certain countries until we have obtained required approvals or exemptions in the individual country. The regulatory review process varies from country to country, and approval by foreign governmental authorities is unpredictable, uncertain and generally expensive. Our ability to market our potential products could be substantially limited due to delays in receipt of, or failure to receive, the necessary approvals or clearances. We anticipate commencing the applications required in some or all of these countries following approval by the FDA; however, we may decide to file applications in advance of the FDA approval if we determine such filings to be both time and cost effective. If we export any of our potential products or products that have not yet been cleared for commercial distribution in the United States, such products may be subject to FDA export restrictions. Failure to obtain necessary regulatory approvals could impair our ability to generate revenue from international sources.

Market acceptance of our X-22 smoking cessation aid could be limited if users are unable to obtain adequate reimbursement from third-party payers.

Government health administration authorities, private health insurers and other organizations generally provide reimbursement for FDA-approved smoking cessation products, and our commercial success could depend in part on these third-party payers agreeing to reimburse patients for the costs of our *X-22* smoking cessation aid. Even if we succeed in bringing our *X-22* smoking cessation aid to market, there is no assurance that third-party payers will consider *X-22* cost effective or provide reimbursement in whole or in part for its use.

Significant uncertainty exists as to the reimbursement status of newly approved health care products. Our *X-22* smoking cessation aid is intended to replace or alter existing therapies or procedures. These third-party payers may conclude that our *X-22* smoking cessation aid is less safe, effective or cost-effective than these existing therapies or procedures. Therefore, third-party payers may not approve *X-22* for reimbursement.

If third-party payers do not approve our potential products for reimbursement or fail to reimburse for them adequately, sales could suffer as some physicians or their patients could opt for a competing product that is approved for reimbursement or is adequately reimbursed. Even if third-party payers make reimbursement available, these payers' reimbursement policies may adversely affect our ability and the ability of our potential collaborators to sell our potential products on a profitable basis.

The trend toward managed healthcare in the United States and, the Affordable Care Act enacted on March 23, 2010, and legislative proposals to reform healthcare and government insurance programs could significantly influence the purchase of healthcare services and products, resulting in lower prices and reduced demand for our potential products which could adversely affect our business, financial condition, results of operations and cash flows.

In addition, legislation and regulations affecting the pricing of our potential products may change in ways adverse to us before or after the FDA or other regulatory agencies approve any of our potential products for marketing. While we cannot predict the likelihood of any of these legislative or regulatory proposals, if any government or regulatory agency adopts these proposals, they could materially adversely affect our business, financial condition, results of operations and cash flows.

Our clinical trials for any of our potential products may produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional clinical and/or preclinical testing for these potential products or cease our trials.

We do not know whether clinical trials of our potential products will demonstrate safety and efficacy sufficiently to result in marketable products. Because our clinical trials for our *X-22* smoking cessation aid and any other potential products may produce negative or inconclusive results, we may decide, or regulators may require us, to conduct additional clinical and/or preclinical testing for these potential products or cease our clinical trials. If this occurs, we may not be able to obtain approval or marketing authorization for these potential products or our anticipated time of bringing these potential products to the market may be substantially delayed and we may also experience significant additional development costs. We may also be required to undertake additional clinical testing if we change or expand the indications for our potential products.

Risks Related to the Tobacco Industry

Our business faces significant governmental action aimed at increasing regulatory requirements with the goal of preventing the use of tobacco products.

Cigarette companies face significant governmental action, especially in the United States pursuant to the Tobacco Control Act, including efforts aimed at reducing the incidence of tobacco use, restricting marketing and advertising, imposing regulations on packaging, warnings and disclosure of flavors or other ingredients, prohibiting the sale of tobacco products with certain flavors or other characteristics, limiting or prohibiting the sale of tobacco products by certain retail establishments and the sale of tobacco products in certain packaging sizes, and seeking to hold retailers and distributors responsible for the adverse health effects associated with both smoking and exposure to environmental tobacco smoke. Governmental actions, combined with the diminishing social acceptance of smoking and private actions to restrict smoking, have resulted in reduced industry volume in the United States and certain other countries, and we expect that these factors will continue to reduce consumption levels in these countries.

Certain of such actions may have a favorable impact on our *X-22* smoking cessation aid, or on our *BRAND A* and *BRAND B* cigarettes if we are able to market them as Modified Risk Cigarettes. However, there is no assurance of such favorable impact and such actions may have a negative impact on our ability to market *RED SUN* and *MAGIC*.

Significant regulatory developments will take place over the next few years in many markets, driven principally by the World Health Organization’s Framework Convention on Tobacco Control (“FCTC”). The FCTC is the first international public health treaty on tobacco, and its objective is to establish a global agenda for tobacco regulation with the purpose of reducing initiation of tobacco use and encouraging cessation. In addition, the FCTC has led to increased efforts by tobacco control advocates and public health organizations to reduce the appeal of tobacco products. Partly because of some or a combination of these efforts, unit sales of tobacco products in certain markets, principally Western Europe and Japan, have been in general decline and we expect this trend to continue. Our operating results could be significantly affected by any significant decrease in demand for cigarettes, any significant increase in the cost of complying with new regulatory requirements and requirements that lead to a commoditization of tobacco products such as the 2012 implementation of plain packaging in Australia.

If implemented in the future, the FDA requirement regarding graphic health warnings on cigarette packaging and in cigarette advertising is likely to have a negative impact on sales of our products.

In November 2010, as required by the Tobacco Control Act, the FDA issued a proposed rule to modify the required warnings that appear on cigarette packages and in cigarette advertisements. These warning were finalized on June 21, 2011 and consist of nine new textual warning statements accompanied by color graphics depicting the negative health consequences of smoking. The FDA selected nine images from the originally proposed 36 images after reviewing the relevant scientific literature, analyzing the results from an 18,000 person study and considering more than 1,700 comments from a variety of groups. The graphic health warnings will be located beneath the cellophane wrapping on cigarette packages, and will comprise the top 50 percent of the front and rear panels of cigarette packages. The graphic health warnings will occupy 20 percent of a cigarette advertisement and will be located at the top of the advertisement. Each warning is accompanied by a smoking cessation phone number, 1-800-QUIT-NOW. Although these graphic health warnings were supposed to be implemented in September 2012, a federal judge ruled that these warnings are unconstitutional. If and when these graphic health warnings are implemented, all cigarettes manufactured for sale or distribution in the United States will need to include these new graphic health warnings on their packages. Any reduction in the number of smokers will probably reduce the demand for *MAGIC* and *RED SUN*, as well as *X-22*, *BRAND A* and *BRAND B*, if and when approved/authorized by the FDA. *MAGIC*, *RED SUN*, *BRAND A* and *BRAND B* will be subject to these new packaging and advertising regulations. It is unclear at this time whether the FDA may require *X-22 and SPECTRUM* to be subject to these new packaging and advertising regulations.

We may become subject to litigation related to cigarette smoking and exposure to environmental tobacco smoke, or ETS, which could severely impair our results of operations and liquidity.

Although we are not currently subject to legal proceedings, we may become subject to litigation related to the sale of our *RED SUN* and *MAGIC* cigarettes and, upon FDA authorization, our *BRAND A* and *BRAND B* cigarettes. Legal proceedings covering a wide range of matters related to tobacco use are pending or threatened in various U.S. and foreign jurisdictions. Various types of claims are raised in these proceedings, including product liability, consumer protection, antitrust, tax, contraband shipments, patent infringement, employment matters, claims for contribution and claims of competitors and distributors.

Litigation is subject to uncertainty and it is possible that there could be adverse developments in pending cases. An unfavorable outcome or settlement of pending tobacco related litigation could encourage the commencement of additional litigation. The variability in pleadings, together with the actual experience of management in litigating claims, demonstrates that the monetary relief that may be specified in a lawsuit bears little relevance to the ultimate outcome.

Damages claimed in some tobacco-related litigation are significant and, in certain cases range into the billions of dollars. We anticipate that new cases will continue to be filed. The FCTC encourages litigation against tobacco

product manufacturers. It is possible that our results of operations, cash flows or financial position could be materially affected by an unfavorable outcome or settlement of litigation.

Cigarettes are subject to substantial taxes. Significant increases in cigarette-related taxes have been proposed or enacted and are likely to continue to be proposed or enacted in numerous jurisdictions. These tax increases may affect our sales and profitability and make us less competitive versus certain of our competitors.

Tax regimes, including excise taxes, sales taxes and import duties, can disproportionately affect the retail price of manufactured cigarettes versus other tobacco products, or disproportionately affect the relative retail price of our *RED SUN* and *MAGIC* cigarettes and, upon FDA authorization, our *BRAND A* and *BRAND B* cigarettes versus lower-priced cigarette brands manufactured by our competitors. Increases in cigarette taxes are expected to continue to have an adverse impact on sales of cigarettes resulting in (i) lower consumption levels, (ii) a shift in sales from manufactured cigarettes to other tobacco products or to lower-price cigarette categories, (iii) a shift from local sales to legal cross-border purchases of lower price products, and (iv) illicit products such as contraband and counterfeit.

We may become subject to governmental investigations on a range of matters.

Tobacco companies are often subject to investigations, including allegations of contraband shipments of cigarettes, allegations of unlawful pricing activities within certain markets, allegations of underpayment of custom duties and/or excise taxes, and allegations of false and misleading usage of descriptors such as “lights” and “ultra lights.” We cannot predict the outcome of any to which we may become subject, and we may be materially affected by an unfavorable outcome of future investigations.

Risks Related to Intellectual Property

Our proprietary rights may not adequately protect our intellectual property, products and potential products, and if we cannot obtain adequate protection of our intellectual property, products and potential products, we may not be able to successfully market our products and potential products.

Our commercial success will depend in part on obtaining and maintaining intellectual property protection for our technologies, products and potential products. We will only be able to protect our technologies, products and potential products from unauthorized use by third parties to the extent that valid and enforceable patents cover them, or other market exclusionary rights apply.

The patent positions of life sciences companies, like ours, can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The general patent environment outside the United States also involves significant uncertainty. Accordingly, we cannot predict the breadth of claims that may be allowed or that the scope of these patent rights could provide a sufficient degree of future protection that could permit us to gain or keep our competitive advantage with respect to these products and technology. Additionally, life science companies like ours are often dependent on creating a pipeline of products. We may not be able to develop additional potential products or proprietary technologies that produce commercially viable products or that are themselves patentable.

Although there are currently no challenges to any portion of our intellectual property, our issued patents may be subject to challenge and possibly invalidated by third parties. Changes in either the patent laws or in the interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. In addition, others may independently develop similar or alternative products and technologies that may be outside the scope of our intellectual property. Should third parties obtain patent rights to similar products or technology, this may have an adverse effect on our business.

We also rely on trade secrets to protect our technology, products and potential products, especially where we do not believe patent protection is appropriate or obtainable. Trade secrets, however, are difficult to protect. While we believe that we use reasonable efforts to protect our trade secrets, our own or our strategic partners' employees, consultants, contractors or advisors may unintentionally or willfully disclose our information to competitors. We seek to protect this information, in part, through the use of non-disclosure and confidentiality agreements with employees, consultants, advisors and others. These agreements may be breached, and we may not have adequate remedies for a breach. In addition, we cannot ensure that those agreements will provide adequate protection for our trade secrets, know-how or other proprietary information or prevent their unauthorized use or disclosure.

To the extent that consultants or key employees apply technological information independently developed by them or by others to our products and p