

Synthetic Biologics, Inc.  
Form S-3  
April 29, 2013

**As filed with the Securities and Exchange Commission on April 29, 2013 Registration No. 333-**

**UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

**Washington, D.C. 20549**

**FORM S-3**

**REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933**

**SYNTHETIC BIOLOGICS, INC.**

*(Exact Name of Registrant as Specified in Its Charter)*

**Nevada**

**13-3808303**

*(State or Other Jurisdiction of (I.R.S. Employer*

*Incorporation or Organization) Identification Number)*

**155 Gibbs Street, Suite 412  
Rockville, Maryland 20850**

**(734) 332-7800**

*(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)*

**Jeffrey Riley**

**Chief Executive Officer and President**

**Synthetic Biologics, Inc.**

**155 Gibbs Street, Suite 412  
Rockville, Maryland 20850**

**(734) 332-7800**

*(Name, Address, Including Zip Code, and Telephone Number, Including Area Code of Agent for Service)*

***With copies to:***

**Leslie Marlow, Esq.**

**Gracin & Marlow, LLP**

**405 Lexington Avenue, 26th Floor**

**New York, New York 10174**

**(212) 907-6457**

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this registration statement.

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

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If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. "

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. "

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer    Accelerated filer    Non-accelerated filer    Smaller reporting company  
(Do not check if a smaller reporting company)    b

**CALCULATION OF REGISTRATION FEE**

<b>Title of Each Class of Securities to be Registered</b>	<b>Amount to be Registered (1)(2)(3)</b>	<b>Proposed Maximum Offering Price per Security(4)</b>	<b>Proposed Maximum Aggregate Offering Price</b>	<b>Amount of Registration Fee(5)</b>
Common stock, par value \$.001 per share	10,788,065 shares	\$ 1.53	\$16,505,739	\$ 2,251.39

(1) There is also being registered hereunder an indeterminate number of additional shares of common stock as shall be issuable pursuant to Rule 416 to prevent dilution resulting from stock splits, stock dividends or similar transactions.

(2) Includes (a) 10,152,210 shares of common stock currently outstanding and (b) 635,855 shares of common stock issuable upon exercise of warrants.

Includes an aggregate of 4,110,855 shares of common stock previously registered on the registrant's Registration Statements of Form S-1 (Reg. No. 333-185457), of which 635,855 shares of common stock are issuable upon (3) exercise of warrants.

Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457(c) of the Securities Act based upon a \$1.53 per share average of high and low prices of the registrant's common stock on the (4) NYSE MKT on April 26, 2013.

(5) A fee of \$1,321.50 is being paid with the filing of this registration statement. The fee relates to 6,677,210 shares of common stock. A fee of \$929.89 that included 3,475,000 shares of common stock outstanding and 635,855 shares of common stock underlying warrants was previously paid in connection with the registrant's Registration Statements on Form S-1 (Reg. No. 333-185457).

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The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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Pursuant to Rule 429 of the Securities Act of 1933, the prospectus included in this registration statement also relates to certain unsold securities of the registrant registered under Registration Statement No. 333-185457.

**EXPLANATORY NOTE**

This registration statement on Form S-3 includes an aggregate of 4,110,855 shares of common stock of the registrant previously registered on Registration Statement on Form S-1, File No. 333-185457 (the "Prior Registration Statement"), originally filed with the Securities and Exchange Commission on December 13, 2012 and subsequently declared effective, which includes 635,855 shares of registrant's common stock underlying certain warrants. Pursuant to Rule 429 under the Securities Act of 1933, as amended, this registration statement, upon effectiveness, will serve as a post-effective amendment to the Prior Registration Statement. Accordingly, this registration statement carries forward from the Prior Registration Statement an aggregate of 4,110,855 shares of common stock. In addition, this registration statement registers for resale by certain selling stockholders an additional 6,677,210 shares of common stock which have not been previously registered.

**The information contained in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.**

**PROSPECTUS SUBJECT TO COMPLETION, DATED APRIL 29, 2013**

10,788,065 Shares

Common Stock

This prospectus relates to the resale by the investors listed in the section titled “Selling Stockholders”, and we refer to the investors as the Selling Stockholders (the “Selling Stockholders”) of up to 10,788,065 shares of our common stock, par value \$0.001 per share (the “Shares”), of which 10,152,210 shares of common stock are currently outstanding and 635,855 shares of common stock are issuable upon exercise of warrants (the “Warrants”). The Shares and Warrants were acquired by the Selling Stockholders in connection with a private placement offering we completed on October 30, 2012 (the “October 2012 Private Placement”) and the Second Channel Agreement and the related Stock Issuance Agreement with Intrexon Corporation (“Intrexon”) that we entered into on August 6, 2012 (the “Second Stock Issuance Agreement”).

We are filing the registration statement of which this prospectus forms a part in order to fulfill contractual obligations that we have to the Selling Stockholders. All of the outstanding Shares and Warrants described above were previously issued in private placement transactions completed prior to the filing of the registration statement of which this prospectus forms a part. We will not receive any proceeds from the disposition of such shares.

Our common stock is traded on NYSE MKT under the symbol “SYN”. On April 26, 2013, the last reported sale price for the common stock was \$1.53 per share. We urge prospective purchasers of our common stock to obtain current information about the market prices of our common stock. The prices at which the selling stockholders may sell the shares of common stock in this offering will be determined by the prevailing market price for the shares of common stock or in negotiated transactions.

Our executive offices are located at 155 Gibbs Street, Suite 412, Rockville, Maryland 20850. Our telephone number is (734) 332-7800.

**Investing in our common stock involves risks. Risks associated with an investment in our common stock are described in “Risk Factors” on page 10.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of the prospectus. Any representation to the contrary is a criminal offense.**

The date of this prospectus is April 29, 2013.



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**The registration statement containing this prospectus, including the exhibits to the registration statement, provides additional information about us and the common stock offered under this prospectus. The registration statement, including the exhibits and the documents incorporated herein by reference, can be read on the Securities and Exchange Commission website or at the Securities and Exchange Commission offices mentioned under the heading “Where You Can Find More Information.”**

## ABOUT THIS PROSPECTUS

This prospectus is not an offer or solicitation in respect to these securities in any jurisdiction in which such offer or solicitation would be unlawful. This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission. The registration statement that contains this prospectus (including the exhibits to the registration statement) contains additional information about our company and the securities offered under this prospectus. That registration statement can be read at the Securities and Exchange Commission website or at the Securities and Exchange Commission's offices listed under the heading "Where You Can Find More Information." We have not authorized anyone else to provide you with different information or additional information. You should not assume that the information in this prospectus, or any supplement or amendment to this prospectus, is accurate at any date other than the date indicated on the cover page of such documents.

## PROSPECTUS SUMMARY

### Our Business

We are a biotechnology company focused on the development of biologics for the prevention and treatment of serious infectious diseases. We are developing an oral enzyme for the prevention of *C. difficile* infections, and a series of monoclonal antibody therapies for the treatment of Pertussis and *Acinetobacter* infections. In addition, we are developing a drug candidate for the treatment of relapsing-remitting multiple sclerosis and cognitive dysfunction in multiple sclerosis, and have partnered the development of a treatment for fibromyalgia.

### *Product Pipeline:*

### *Summary of Infectious Disease Programs:*

***Clostridium difficile* (*C. difficile*) infections:** In November 2012, we acquired a series of oral beta-lactamase enzymes (P1A, P2A and P3A) and related assets targeting the prevention of *C. difficile* infections (CDI), the leading cause of hospital acquired infections (HAI), that generally occurs secondary to treatment with intravenous antibiotics. The acquired assets include a pre-Investigational New Drug (IND) package for P3A (SYN-004), Phase I and Phase II clinical data for P1A, manufacturing processes and data, and a portfolio of issued and pending U.S. and international

patents intended to support an IND and Biologic License Application (BLA) with the FDA. Utilizing this portfolio of assets, we intend to develop a proprietary oral beta-lactamase enzyme product candidate, SYN-004, previously known as IPSAT P3A. When co-administered with certain intravenous beta-lactam antibiotics, it is expected that SYN-004 can degrade the antibiotic that is excreted in the gastrointestinal (GI) tract, thus preserving the natural balance of the patient's microflora, and preventing opportunistic infections including CDI. Beta-lactam antibiotics are a mainstay in hospital infection management and include the commonly used penicillin and cephalosporin classes of antibiotics. According to GlobalData, an estimated 8.7 million Americans were administered intravenous beta-lactam antibiotics in 2011.

**Pertussis:** In December 2012, in collaboration with Intrexon, we initiated development of a monoclonal antibody (mAb) therapy for the treatment of Pertussis infections, more commonly known as whooping cough. We are developing a mAb therapy, SYN-005, designed to target and neutralize the pertussis toxin, in order to reduce the mortality rate in infants and potentially shorten the duration of chronic cough in afflicted adults. To further the development of this potential therapy for Pertussis, we entered into an agreement with The University of Texas at Austin to license the rights to certain research and pending patents related to pertussis antibodies. According to the World Health Organization, each year, *B. pertussis* infection causes an estimated 294,000 deaths worldwide, primarily among young, unvaccinated children.

**Acinetobacter infections:** In September 2012, in collaboration with Intrexon, we initiated efforts to develop a mAb therapy for the treatment of *Acinetobacter* infections. Many strains of *Acinetobacter* are multidrug-resistant and pose an increasing global threat to hospitalized patients, wounded military personnel and those affected by natural disasters. A treatment for *Acinetobacter* infections represents a multi-billion dollar market opportunity.

*Summary of Multiple Sclerosis Program:*

- Trimesta™ (oral estriol) is being developed as an oral once-daily treatment for relapsing-remitting multiple sclerosis (MS) in women. Patient enrollment is complete in this two-year, randomized, double-blind, placebo-controlled Phase II clinical trial being conducted at 15 centers in the U.S. The primary endpoint is relapse rate at two years, with top-line results expected in 1H 2014. This trial is supported by grants exceeding \$8 million, which should be sufficient to fund the trial through completion. Current sales of injectable disease-modifying therapies for MS are estimated at \$8.9 billion annually.

Trimesta™ is also being developed for the treatment of cognitive dysfunction in female MS patients. This 12-month randomized, double-blind, placebo-controlled Phase II clinical trial being conducted at University of California, Los Angeles (UCLA). The primary endpoint is the effect on cognitive function as assessed by Paced Auditory Serial Addition Test (PASAT). Patient enrollment is ongoing. The majority of the costs of this trial are being funded by grants from foundations and charitable organizations and we have pledged approximately \$500,000 to UCLA to partially fund this trial payable over three years. An estimated 50-65% of MS patients are expected to develop disabilities due to cognitive dysfunction and there is currently no approved treatment.

*Summary of Fibromyalgia Program:*

Effirma™ (flupirtine) is being developed for the treatment of fibromyalgia by Meda AB (Meda), a multi-billion dollar international pharmaceutical company. On May 6, 2010, we entered into a sublicense agreement with Meda covering all of our patents' rights on the use of flupirtine for fibromyalgia in the U.S., Canada and Japan. The sublicense agreement provides that all ongoing and future development costs are to borne by Meda and we are entitled to receive certain payments if milestones are achieved and royalties on sales. According to Meda's 2012 Year-End Report filed in February 2013, Meda has received the go-ahead from the FDA to conduct a Phase II proof of concept study for the treatment of fibromyalgia. Meda also announced that the randomized, double-blind, placebo

and active-controlled study of patients with fibromyalgia will be conducted at 25 clinics in the U.S. Based on an estimated annual price of \$1,200 per fibromyalgia patient, we estimate that the total market potential in the U.S. is \$6 billion.

In order to further prioritize our focus, we have elected to discontinue further development of AEN-100 for the treatment of amyotrophic lateral sclerosis. However, we are currently seeking development partners for our zinc-based intellectual property and assets including, AEN-100.

## **Pipeline Programs and Therapeutic Areas**

### **Infectious Disease Programs**

We are focused on the development of biologics for the prevention and treatment of serious infectious diseases. Infectious disease outbreaks are increasing while intervention options are declining due to widespread multidrug-resistant bacteria, increasing numbers of immuno-compromised patients (eg. the elderly and cancer patients), and the isolation of new pathogens. We are developing an oral enzyme for the prevention of *C. difficile* infections, and a series of monoclonal antibody therapies for the treatment of Pertussis and *Acinetobacter* infections.

***C. difficile Infections:***

According to the Agency for Healthcare Research and Quality, aggregate costs associated with CDI-related stays in the hospital were \$8.2 billion in the U.S. during 2009. CDI is a rising global HAI problem in which the toxins produced by *C. difficile* bacteria result in diarrhea (*C. difficile*-associated diarrhea (CDAD)), and in the most serious cases, pseudomembranous colitis (erosion of the lower GI tract) that can lead to death. CDI is a major, unintended risk associated with the prophylactic or therapeutic use of intravenous antibiotics, which may alter the natural balance of microflora that normally protect the GI tract, leading to *C. difficile* overgrowth and infection. Other risk factors for CDI include hospitalization, prolonged length of stay, underlying illness, immune-compromising conditions including the administration of chemotherapy, and advanced age.

CDI is a widespread and often drug resistant infectious disease, resulting in more than 337,000 hospitalizations and 30,000 deaths in the U.S. during 2009, according to the U.S. Department of Health & Human Services. CDI has surpassed methicillin-resistant staphylococcus aureus (MRSA) as the most frequent infection acquired in the hospital. It has recently been reported by The Centers for Disease Control and Prevention that the current number of CDI cases may be as high as 500,000 annually in the U.S. Controlling the spread of CDI has proven challenging, as the *C. difficile* spores are easily transferred to patients via normal contact with healthcare personnel and other inanimate objects. There is currently no vaccine or approved product for the prevention of *C. diff* infection.

***C. difficile: Acquisition of Clinical-Stage Program***

In November 2012, we acquired a series of oral beta-lactamase enzymes (P1A, P2A and P3A) and related assets targeting the prevention CDI, the leading cause of HAIs, that generally occurs secondary to treatment with intravenous antibiotics. The acquired assets include a pre-IND package for P3A (SYN-004), Phase I and Phase II clinical data for P1A, manufacturing processes and data, and a portfolio of issued and pending U.S. and international patents intended to support an IND and BLA with the FDA. Utilizing this portfolio of assets, we intend to develop a proprietary oral beta-lactamase enzyme product candidate, SYN-004, previously known as IPSAT P3A. When co-administered with certain intravenous beta-lactam antibiotics, it is expected that SYN-004 can degrade the antibiotic that is excreted in the GI tract, thus preserving the natural balance of the patient's microflora, and preventing opportunistic infections including CDI. Beta-lactam antibiotics are a mainstay in hospital infection management and include the commonly used penicillin and cephalosporin classes of antibiotics. According to GlobalData, an estimated 8.7 million Americans were administered intravenous beta-lactam antibiotics in 2011.

***C. difficile: Oral Enzyme Background***

We acquired a series of oral beta-lactamase enzymes (P1A, P2A and P3A). Beta-lactamase enzymes have the ability to degrade beta-lactam antibiotics that may be excreted into the GI tract. P1A (the first generation candidate) showed acceptable safety and tolerability in a Phase I study. In addition, two Phase II clinical studies demonstrated that P1A had the ability to preserve GI microflora in hospitalized patients treated with intravenous ampicillin or the combination of piperacillin and tazobactam.

### *C. difficile: Clinical Development*

Compared to the first generation oral enzyme candidate, P1A, we believe that SYN-004 (formerly P3A) will have activity against a broader spectrum of beta-lactam antibiotics, including both penicillins and most cephalosporins. Due to the structural similarities between P1A and SYN-004 for the prevention of CDI, along with previous discussions with the FDA, it is anticipated that certain preclinical data collected on P1A may be used in support of an IND for our new product candidate, SYN-004.

### ***Monoclonal Antibodies:***

#### *Monoclonal Antibodies for Infectious Diseases*

Acting as the body's army, antibodies are proteins, generally found in the bloodstream, that provide immunity in detecting and destroying pathogens, such as viruses and bacteria and their associated toxins. MAbs can also be designed and produced as therapeutic agents, utilizing protein engineering and recombinant production technologies. The mAbs being developed under our collaboration with Intrexon are intended to supplement a patient's own immune system by providing the means to specifically and rapidly neutralize and/or clear specific pathogens and toxins of interest in a process known as "passive immunity". Many pathogens that cause infectious diseases are innately resistant to, or over time have developed increased resistance to, antibiotics and other drugs.

#### *Intrexon Collaboration: Monoclonal Antibodies for Infectious Diseases*

In August 2012, we entered into a worldwide exclusive channel collaboration with Intrexon through which we intend to develop a series of mAb therapies for the treatment of certain infectious diseases not adequately addressed by existing therapies. Utilizing Intrexon's comprehensive suite of proprietary technologies, including the mAbLogix™ platform for rapid discovery of fully human mAbs and the LEAP™ cell processing station, our initial efforts will target three infectious disease indications. We also have the option to target an additional five infectious disease indications under this collaboration. To date, we have initiated development of a mAb therapy for the treatment of Pertussis and *Acinetobacter* infections.





(mAbLogix™ and LEAP™ are registered trademarks of Intrexon Corporation)

*Bordetella pertussis* (*B. pertussis*) is a gram-negative bacterium that infects the upper respiratory tract, causing uncontrollable, violent coughing. Antibiotic treatment does not have a major effect on the course of Pertussis, because while it can eliminate the *B. pertussis* bacteria from the respiratory tract, it does not neutralize the pertussis toxin. Infants with Pertussis often require hospitalization in pediatric intensive care units, frequently requiring mechanical ventilation. Pertussis in adults generally leads to a chronic cough referred to as the "cough of 100 days." The incidence of Pertussis is increasing in association with exposure of unvaccinated and under-vaccinated individuals including infants who are not yet fully vaccinated, exposure of individuals whose immunity has diminished over time, as well as asymptomatic carriers.

According to the World Health Organization, each year, *B. pertussis* infection causes an estimated 294,000 deaths worldwide, primarily among young, unvaccinated children. Recent news reports throughout the U.S. indicate that the pertussis vaccine introduced in the 1990s does not provide long-term protection and, as a result, whooping cough cases are increasing to a 60-year high. There is no approved treatment for Pertussis, and antibiotic treatment does not have a major effect on the course of Pertussis, because while it can eliminate the *B. pertussis* bacteria from the respiratory tract, it does not neutralize the pertussis toxin.

*Pertussis: Intrexon Collaboration and The University of Texas at Austin Agreement*

In December 2012, we initiated mAb development for the treatment of Pertussis focusing on toxin neutralization pursuant to our August 2012 collaboration with Intrexon. Unlike antibiotics, we are developing a mAb therapy, SYN-005, to target and neutralize the pertussis toxin, in order to reduce the mortality rate in infants and potentially shorten the duration of chronic cough in afflicted adults. SYN-005 is currently in preclinical studies.

To further the development of this potential therapy for pertussis, we have entered into an agreement with The University of Texas at Austin to license the rights to certain research and pending patents related to pertussis antibodies. These research efforts are being conducted at the Cockrell School of Engineering in the laboratory of Assistant Professor, Jennifer A. Maynard, Ph.D., the Laurence E. McMakin, Jr. Centennial Faculty Fellow in the McKetta Department of Chemical Engineering. Dr. Maynard brings to the project her expertise in defining the key neutralizing epitopes of pertussis toxin to optimize the potential efficacy of antibody therapeutics.

*Acinetobacter Infections:*

*Acinetobacter baumannii* is a difficult to treat pathogen due to its rapid and well-established development of resistance to most antibiotics, making it a multidrug-resistant pathogen. In addition, as a biofilm-forming pathogen, *Acinetobacter baumannii* has the ability to survive up to twice as long as non-biofilm-forming pathogens. In the U.S., *Acinetobacter baumannii* has been reported to be the cause of up to 2.6% of hospital acquired infections, 1.3% of bloodstream infections and 7% of ICU respiratory tract infections, and more than half of the *Acinetobacter baumannii* isolates are multidrug-resistant. According to published articles, mortality rates as high as 43% are reported in hospital and ICU settings. While *Acinetobacter baumannii* is a well-documented pathogen in the hospital setting, this pathogen also poses an increasing danger to wounded servicemen and women in military treatment centers and to those treated in trauma centers following natural disasters.

A treatment for *Acinetobacter* infections represents a multi-billion dollar market opportunity.

#### *Acinetobacter: Intrexon Collaboration*

In August 2012, we initiated a mAb discovery and development program for *Acinetobacter* infections pursuant to our August 2012 collaboration with Intrexon. Discovery efforts for the development of a mAb are currently underway.

#### **Multiple Sclerosis Program**

##### ***Relapsing-Remitting MS in Women:***

MS is a progressive neurological disease in which the body loses the ability to transmit messages along central nervous system nerve cells, leading to pain, loss of muscle control, paralysis, cognitive impairment and in some cases death. According to the National Multiple Sclerosis Society (NMSS), more than 2.5 million people worldwide (approximately 400,000 patients in the U.S. of which approximately 70% are women) have been diagnosed with MS. The diagnosis is typically made in young adults, ages 20 to 50. According to the NMSS, approximately 85% of MS patients are initially diagnosed with the relapsing-remitting form, and 10-15% with other progressive forms.

There are ten FDA-approved therapies for the treatment of relapsing-remitting MS: Betaseron<sup>®</sup>, Rebif<sup>®</sup>, Avonex<sup>®</sup>, Novantrone<sup>®</sup>, Copaxone<sup>®</sup>, Tysabri<sup>®</sup>, Gilenya<sup>®</sup>, Extavia<sup>®</sup>, Aubagio<sup>®</sup> and Tecfidera<sup>™</sup>. Many of these therapies provide only a modest benefit for patients with relapsing-remitting MS. All of these drugs except Gilenya<sup>®</sup> and Tecfidera<sup>™</sup> require frequent (daily, weekly & monthly) injections (or infusions) on an ongoing basis and can be associated with unpleasant side effects (such as flu-like symptoms) and high rates of non-compliance among users. Despite the availability of therapies for the treatment of relapsing-remitting MS, the disease is highly underserved and exacts a heavy personal and economic toll.

Current sales of injectable disease-modifying therapies for MS are estimated at \$8.9 billion annually. According to various reports, sales of oral disease-modifying therapies for MS, such as Trimesta, if and when approved, are anticipated to grow from \$500 million in 2010 to in excess of \$5 billion annually by 2017.

#### *Relapsing-Remitting MS: Background*

Research has shown that pregnant women with MS tend to experience a spontaneous reduction of disease symptoms during pregnancy, particularly in the third trimester. The PRIMS (Pregnancy In MS) study, a landmark clinical study published in the *New England Journal of Medicine* followed 254 women with MS during 269 pregnancies and for up to one year after delivery. The PRIMS study demonstrated that relapse rates were significantly reduced by 71% ( $p < 0.001$ ) through the third trimester of pregnancy compared to pre-pregnancy-rates, and that relapse rates increased by 120% ( $p < 0.001$ ) during the first three months after birth (post-partum) and then return to pre-pregnancy rates. It has been hypothesized that the female hormone, estriol, produced by the placenta during pregnancy, plays a role in “fetal immune privilege”, a process that prevents a mother’s immune system from attacking and rejecting the fetus. The maternal levels of estriol increase linearly through the third trimester of pregnancy until birth, whereupon it abruptly returns to low circulating levels. The anti-autoimmune effects of estriol are thought to be responsible for the therapeutic effects of pregnancy on MS.

Rhonda Voskuhl, M.D., Director, UCLA MS program, UCLA Department of Neurology, has found that plasma levels of estriol achieved during pregnancy have potent immunomodulatory effects. She further postulated and tested in a pilot clinical study that oral doses of estriol may have a therapeutic benefit when administered to non-pregnant female MS patients by, in essence, mimicking the spontaneous reduction in relapse rates seen in MS patients during pregnancy.

Estriol has been approved and marketed for over 40 years throughout Europe and Asia for the oral treatment of post-menopausal symptoms. It has never been approved by the U.S. FDA for any indication.

#### *Relapsing-Remitting MS: Clinical Development*

Trimesta (oral estriol) is being developed for the treatment of relapsing-remitting MS in women. An investigator-initiated, 10-patient, 22-month, single-agent, crossover clinical trial to study the therapeutic effects of 8 mg of oral Trimesta taken daily in non-pregnant female relapsing-remitting MS patients was completed in the U.S. The total volume and number of gadolinium-enhancing lesions were measured by brain magnetic resonance imaging (an established neuroimaging measure of disease activity in MS). Over the next three months of treatment with Trimesta, the median total enhancing lesion volumes decreased by 79% ( $p = 0.02$ ) and the number of lesions decreased by 82% ( $p = 0.09$ ). They remained decreased during the next 3 months of treatment, with lesion volumes decreased by 82% ( $p = 0.01$ ), and numbers decreased by 82% ( $p = 0.02$ ). Following a six-month drug holiday during which the patients were not on any drug therapies, median lesion volumes and numbers returned to near baseline pretreatment levels. Trimesta therapy was reinitiated during a four-month retreatment phase of this clinical trial. The relapsing-remitting MS patients again demonstrated a decrease in enhancing lesion volumes of 88% ( $p = 0.008$ ) and a decrease in the number of lesions by 48% ( $p = 0.04$ ) compared with original baseline scores.

A Phase II randomized, double-blind, placebo-controlled clinical trial is currently underway at 15 centers in the U.S. under the direction of Lead Principal Investigator, Dr. Rhonda Voskuhl. The purpose of this clinical trial is to evaluate whether 8 mg of oral Trimesta taken daily over a two year period will reduce the rate of relapses in a large population of female patients with relapsing-remitting MS. Investigators are administering either Trimesta or matching placebo, in addition to a standard of care, glatiramer acetate injections (Copaxone<sup>®</sup>), an FDA-approved therapy for MS, to women between the ages of 18 to 50 who have been recently diagnosed with relapsing-remitting MS. Relapse rates at two years is the primary endpoint in this clinical trial being run under an investigator-initiated IND. As of January 23, 2012, 164 patients have been enrolled and enrollment has been closed. The patients will be dosed and monitored for two years with the last patient scheduled to complete two years of therapy in January 2014.

With over \$8 million in grant funding to date, the ongoing Trimesta clinical trial should be funded to its completion.

### *Cognitive Dysfunction in MS:*

According to the NMSS and the Multiple Sclerosis Society of Canada publication, *Hold that Thought! Cognition and MS*, it is fairly common for people with MS to complain of cognitive difficulties, such as remembering things, finding the right words and the ability to concentrate. Among MS patients, 50-65% have some degree of cognitive dysfunction.

The major areas of cognition that may be affected include complex attention and executive functions. Complex attention involves multitasking, the speed with which information can be processed, learning and memory, and perceptual skills; executive functions include problem solving, organizational skills, the ability to plan, and word finding. Just as the nature, frequency, and severity of MS-related physical problems can widely vary, not all people with MS will have cognitive dysfunction, and no two people will experience exactly the same type or severity.

### *Cognitive Dysfunction in MS: Background*

In the investigator-initiated, 10-patient, 22-month, single-agent, crossover clinical trial conducted by Dr. Rhonda Voskuhl, a statistically significant 14% improvement from baseline in the PASAT cognitive testing scores ( $p = 0.04$ ) was observed in relapsing-remitting MS patients after six months of Trimesta therapy. PASAT is a routine cognitive test performed in patients with a wide variety of neuropsychological disorders such as MS. The PASAT scores are expressed as a mean percent change from baseline.

### *Cognitive Dysfunction in MS: Clinical Development*

Our Trimesta (oral estriol) drug candidate is also being developed for the treatment of cognitive dysfunction in female MS patients. This randomized, double-blind, placebo-controlled Phase II clinical trial to evaluate Trimesta's potential neuroprotective and therapeutic effect on cognitive dysfunction in female MS patients is currently enrolling relapsing-remitting or secondary-progressive female MS patients at UCLA. Up to 64 patients between the ages of 18 and 50 will be randomized 1:1 into the treatment and placebo groups. Dr. Voskuhl will administer either oral Trimesta or a matching placebo, in addition to any FDA-approved MS treatment. Each patient will be dosed and monitored for one year after being enrolled. The primary endpoint in this clinical trial being run under an investigator-initiated IND application is expected to be improvement in PASAT cognitive testing scores versus matching placebo. We and a private foundation have pledged to equally support this new clinical trial, and we will also provide Trimesta drug supply. The trial also received contributions from several other supporters. Patient recruitment and enrollment into this trial is ongoing.

**Fibromyalgia Program**

Fibromyalgia is a chronic and debilitating condition characterized by widespread pain and stiffness throughout the body, often accompanied by severe fatigue, insomnia and alterations in mood. According to the National Fibromyalgia Association, fibromyalgia affects an estimated 3-6% of the population worldwide, including an estimated 10 million people in the U.S. There are presently three FDA products approved for the treatment of fibromyalgia – Lyrica®, Cymbalta® and Savella®.

Based on an estimated annual price of \$1,200 per fibromyalgia patient, we estimate that the total market potential in the U.S. is \$6 billion.

*Fibromyalgia: Meda Corporate Partnership*

On May 6, 2010, we entered into a sublicense agreement with Meda, a multi-billion dollar international pharmaceutical company, pursuant to which Meda assumed all future development costs and may commercialize flupirtine, a molecular entity with a unique mode of action for the treatment fibromyalgia in the U.S. As consideration for such sublicense, we received an up-front payment of \$2.5 million and are entitled to milestone payments of \$5 million upon the FDA's acceptance of the New Drug Application (NDA) for flupirtine for fibromyalgia and \$10 million upon FDA approval of such NDA. Pursuant to the sublicense agreement, we will also receive a 7% royalty on net sales of flupirtine for fibromyalgia in the U.S., Canada and Japan, with such royalties being shared equally with our licensor, McLean Hospital, a Harvard teaching hospital.

Flupirtine is approved and marketed by Meda and its distributors in Europe and other countries for indications other than fibromyalgia and has been prescribed to millions of patients worldwide. We believe that such substantial human experience with flupirtine should greatly assist the FDA in its evaluation of the safety of flupirtine upon review of an NDA of flupirtine for fibromyalgia.

### *Fibromyalgia: Clinical Development*

Our Effirma (flupirtine) drug candidate for the treatment of fibromyalgia, has been partnered to Meda (see “Fibromyalgia: Meda Corporate Partnership” section above). Effirma is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Effirma is a non-opioid, non-NSAID, non-steroidal, analgesic. Preclinical data and clinical experience suggest that Effirma should also be effective for neuropathic pain since it acts in the central nervous system via a mechanism of action distinguishable from most marketed analgesics. Effirma is especially attractive because it operates through non-opiate pain pathways, exhibits no known abuse potential, and lacks withdrawal effects. In addition, no tolerance to its antinociceptive effects has been observed. One common link between neuroprotection, nociception and Effirma may be the N-methyl-D-aspartic acid glutamate system, a major receptor subtype for the excitotoxic neurotransmitter, glutamate. Effirma has strong inhibitory actions on N-methyl-D-aspartic acid-mediated neurotransmission. Flupirtine was originally developed by Asta Medica (subsequently acquired by Meda) and has been approved and is marketed by Meda in Europe since 1984, as well as other countries, for the treatment of pain. It has never been approved by the FDA for any indication.

According to Meda’s 2012 Year-End Report filed in February 2013, Meda has received the go-ahead from the FDA to conduct a Phase II proof of concept study for the treatment of fibromyalgia. Meda also announced that the randomized, double-blind, placebo and active-controlled study of patients with fibromyalgia will be conducted at 25 clinics in the U.S.

### **RISK FACTORS THAT MAY AFFECT FUTURE RESULTS**

*An investment in our common stock involves a high degree of risk. You should carefully consider the risks described below and the other information before deciding to invest in our common stock. The risks described below are not the only ones facing our company. Additional risks not presently known to us or that we currently consider immaterial may also adversely affect our business. We have attempted to identify below the major factors that could cause differences between actual and planned or expected results, but we cannot assure you that we have identified all of those factors.*

*If any of the following risks actually happen, our business, financial condition and operating results could be materially adversely affected. In this case, the trading price of our common stock could decline, and you could lose all or part of your investment.*

### **RISKS RELATING TO OUR BUSINESS**

***We will need to raise additional capital to operate our business.***

With the exception of the three months ended June 30, 2010, we have experienced significant losses since inception and have a significant accumulated deficit. We expect to incur additional operating losses in the future and therefore our cumulative losses to increase. To date, other than the licensing fee we received from Meda AB for the development and commercialization of Effirma (flupirtine) for fibromyalgia in the U.S., Canada and Japan and limited laboratory revenues from Adeona Clinical Laboratory, which we sold in March 2012, we have generated very minimal revenues. Inasmuch as our sole source of revenue (with the exception of the Meda licensing fee) has been our laboratory revenue and our laboratory was sold recently, we do not expect to derive revenue from any source in the near future until we or our partners successfully commercialize our products. As of December 31, 2012, our accumulated deficit totaled approximately \$68.9 million on a consolidated basis. Until such time as we receive approval from the FDA and other regulatory authorities for our product candidates, we will not be permitted to sell our products and therefore will not have product revenues from the sale of products. For the foreseeable future we will have to fund all of our operations and capital expenditures from equity and debt offerings, cash on hand, licensing fees and grants. If our current cash, cash equivalents and short-term investments are not sufficient to sustain our operations, we will need to seek additional sources of financing and such additional financing may not be available on favorable terms, if at all. If we do not succeed in raising additional funds on acceptable terms, we may be unable to complete planned preclinical and clinical trials or obtain approval of our product candidates from the FDA and other regulatory authorities. In addition, we could be forced to delay, discontinue or curtail product development, forego sales and marketing efforts, and forego licensing in attractive business opportunities. Any additional sources of financing will likely involve the issuance of our equity or debt securities, which will have a dilutive effect on our stockholders.

***We have not been able to sustain profitability.***

Other than with respect to the three months ended June 30, 2010, we have a history of losses and we have incurred and continue to incur substantial losses and negative operating cash flow. Even if we succeed in developing and commercializing one or more of our product candidates, we may still incur substantial losses for the foreseeable future and may not sustain profitability. We also expect to continue to incur significant operating and capital expenditures and anticipate that our expenses will substantially increase in the foreseeable future as we do the following:

- continue to undertake preclinical development and clinical trials for our product candidates;
- expand our research activities with Intrexon relating to monoclonal antibodies for infectious diseases;
- seek regulatory approvals for our product candidates;



develop our product candidates for commercialization;  
implement additional internal systems and infrastructure;  
lease additional or alternative office facilities; and  
hire additional personnel, including members of our management team.

We may experience negative cash flow for the foreseeable future as we fund our technology development with capital expenditures. As a result, we will need to generate significant revenues in order to achieve and maintain profitability. We may not be able to generate these revenues or achieve profitability in the future. Our failure to achieve or maintain profitability could negatively impact the value of our common stock and underlying securities.

***Our research and development efforts may not succeed in developing commercially successful products and technologies, which may limit our ability to achieve profitability.***

We must continue to explore opportunities that may lead to new products and technologies. To accomplish this, we must commit substantial efforts, funds, and other resources to research and development. A high rate of failure is inherent in the research and development of new products and technologies. Any such expenditures that we make will be made without any assurance that our efforts will be successful. Failure can occur at any point in the process, including after significant funds have been invested.

Regardless of whether our clinical trials are deemed to be successful, promising new product candidates may fail to reach the market or may only have limited commercial success because of efficacy or safety concerns, failure to achieve positive clinical outcomes, inability to obtain necessary regulatory approvals or satisfy regulatory criteria, limited scope of approved uses, excessive costs to manufacture, the failure to establish or maintain intellectual property rights, or infringement of the intellectual property rights of others. Even if we successfully develop new products or enhancements, they may be quickly rendered obsolete by changing customer preferences, changing industry standards, or competitors' innovations. Innovations may not be quickly accepted in the marketplace because of, among other things, entrenched patterns of clinical practice or uncertainty over third-party reimbursement. We cannot state with certainty when or whether any of our products under development will be launched, whether we will be able to develop, license, or otherwise acquire drug candidates or products, or whether any products will be commercially successful. Failure to launch successful new products or new indications for existing products may cause our products to become obsolete, which may limit our ability to achieve profitability.

***The technology on which our channel partnering arrangement with Intrexon is based on early stage technology.***

On August 8, 2012, we announced an exclusive channel collaboration with Intrexon relating to the design, production, testing and commercialization of monoclonal antibodies for the treatment of certain infectious diseases. Although monoclonal antibody therapeutics are well established in the biotechnology and pharmaceutical sectors, their use for

the treatment of infectious disease is extremely limited. In order for monoclonal antibodies to be effective for infectious diseases, they must not only properly target the organism of interest (or its toxins), but may also need to overcome defenses and forms of resistance of such organisms. To accomplish this may require the use of more than one specific monoclonal antibody, and mixtures of different monoclonal antibodies, which may create additional unforeseen complications, including increased manufacturing complexity and expense. In order to be competitive, monoclonal antibodies will be required to be produced at a low enough cost of goods in order to be profitably marketed. We have very limited development and manufacturing experience in the field of monoclonal antibodies and infectious disease. We cannot assure that any monoclonal antibody candidates will provide satisfactory in vitro and in vivo nonclinical results sufficient to warrant the expense of cGMP manufacture and clinical testing in human clinical trials.

*We may not generate additional revenue from our relationships with our corporate collaborators.*

On May 6, 2010, we entered into a sublicense agreement with Meda AB whereby we may receive milestone payments totaling \$17.5 million (including an upfront payment of \$2.5 million that has already been received), plus royalties on our flupirtine program. There can be no assurance that Meda AB will successfully develop flupirtine for fibromyalgia in the U.S., Canada or Japan that would allow us to receive such additional \$15 million in milestone payments and royalties on sales in connection with such agreement. The successful achievement of the various milestones set forth in the sublicense agreement is not within our control and we will be dependent upon Meda AB for achievement of such milestones. According to Meda's 2012 Year-End Report filed in February 2013, Meda has received the go-ahead from the FDA to conduct a Phase II proof of concept study for the treatment of fibromyalgia. There can be no assurance that Meda will initiate or successfully complete such planned study.

***We have experienced several management changes.***

We have had significant changes in management in the past few years. Jeffrey Riley was appointed Chief Executive Officer and President on February 3, 2012. Effective February 6, 2012, C. Evan Ballantyne was appointed Chief Financial Officer. James S. Kuo, M.D., served as Chief Executive Officer and President from February 6, 2010 until February 3, 2012. Changes in our key positions, as well as additions of new personnel and departures of existing personnel, can be disruptive, might lead to additional departures of existing personnel and could have a material adverse effect on our business, operating results, financial results and internal controls over financial reporting.

***We may not be able to retain rights licensed to us by others to commercialize key products and may not be able to establish or maintain the relationships we need to develop, manufacture, and market our products.***

In addition to our own patent applications, we also currently rely on licensing agreements with third party patent holders/licensors for our products. We have an exclusive license agreement with the McLean Hospital relating to the use of flupirtine to treat fibromyalgia which was sublicensed to Meda AB and an exclusive license agreement with the Regents of the University of California relating to our Trimesta technology. Each of these agreements requires us or our sublicensee to use our best efforts to commercialize each of the technologies as well as meet certain diligence requirements and timelines in order to keep the license agreement in effect. In the event we or our sublicensee are not able to meet our diligence requirements, we may not be able to retain the rights granted under our agreements or renegotiate our arrangement with these institutions on reasonable terms, or at all. Furthermore, we currently have very limited product development capabilities, and limited marketing or sales capabilities. For us to research, develop, and test our product candidates, we would need to contract with outside researchers, in most cases those parties that did the original research and from whom we have licensed the technologies. Our exclusive channel collaboration agreement with Intrexon provides that Intrexon may terminate each such agreement if we do not perform certain specified requirements, including developing therapies considered superior. Our agreement with The University of Texas allows the University to terminate its agreement if we fail to comply with the terms of the agreement. Our agreement with PreV provides PreV with the right to the return of the assets if we do not perform certain requirements.

We can give no assurances that any of our issued patents licensed to us or any of our other patent applications will provide us with significant proprietary protection or be of commercial benefit to us. Furthermore, the issuance of a patent is not conclusive as to its validity or enforceability, nor does the issuance of a patent provide the patent holder with freedom to operate without infringing the patent rights of others.

***We will incur additional expenses in connection with our exclusive channel collaboration arrangement with Intrexon and our agreement with PreV.***

Pursuant to our exclusive channel collaboration with Intrexon, we are responsible for future research and development expenses of product candidates developed under each such collaboration, the effect of which has and will continue to increase the level of our overall research and development expenses going forward. Our agreement with Prev requires that we initiate certain studies and file an NDA within a certain amount of time, each of which are costly and will require additional expenditures. Although all manufacturing, preclinical studies and human clinical trials are expensive and difficult to design and implement, costs associated with the manufacturing, research and development of biologic product candidates are generally greater in comparison to small molecule product candidates. We have added additional personnel and expect to add additional personnel to support our exclusive channel collaboration with Intrexon, and research and development of our biologic candidate, SYN-004.

Because our biologic programs are relatively new, we have only recently assumed development responsibility and costs associated with such programs. In addition, because development activities in collaboration with Intrexon are determined pursuant to a joint steering committees comprised of Intrexon and ourselves and we have limited experience, future development costs associated this program may be difficult to anticipate and exceed our expectations. Our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, unanticipated technical challenges, changes in the focus and direction of our development activities or adjustments necessitated by changes in the competitive landscape in which we operate. If we are unable to continue to financially support such collaborations due to our own working capital constraints, we may be forced to delay our activities. If we are unable to obtain additional financing on terms acceptable to us or at all, we may be forced to seek licensing partners or discontinue development.

***Developments by competitors may render our products or technologies obsolete or non-competitive.***

Companies that currently sell or are developing both generic and proprietary products to treat multiple sclerosis include: Abbott Biotherapeutics Corporation, Bayer Health Care, Biogen Idec, Genzyme, GlaxoSmithKline Pharmaceuticals, Merck & Co., Pfizer, Novartis, Sanofi and Teva Pharmaceuticals. Companies that currently sell or are developing both generic and proprietary products to treat infectious diseases include: MedImmune, Pfizer, Cubist, Optimer Pharmaceuticals, Symphogen, Merus, GlaxoSmithKline Pharmaceuticals and Merck & Co. Many of our competitors have significant financial and human resources. The infectious disease market is highly competitive with many generic and proprietary intravenous and oral formulations available to physicians and their patients. For our monoclonal antibodies, we currently do not expect to be able to deliver our infectious disease candidates via the oral route and may thus be limited to the in-patient and/or acute treatment setting. In addition, academic research centers may develop technologies that compete with our Trimesta and flupirtine technologies. Should clinicians or regulatory authorities view these therapeutic regimens as more effective than our products, this might delay or prevent us from obtaining regulatory approval for our products, or it might prevent us from obtaining favorable reimbursement rates from payers, such as Medicare, Medicaid, hospitals and private insurers.

***We operate in a highly competitive environment.***

The pharmaceutical and biotechnology industries, including the monoclonal antibody industry, are characterized by rapidly evolving technology and intense competition. Our competitors include major multi-national pharmaceutical companies and biotechnology companies developing both generic and proprietary therapies to treat serious diseases. Many of these companies are well-established and possess technical, human, research and development, financial, and sales and marketing resources significantly greater than ours. In addition, many of our potential competitors have formed strategic collaborations, partnerships and other types of joint ventures with larger, well established industry competitors that afford these companies potential research and development and commercialization advantages in the therapeutic areas we are currently pursuing.

Academic research centers, governmental agencies and other public and private research organizations are also conducting and financing research activities which may produce products directly competitive to those being developed by us. In addition, many of these competitors may be able to obtain patent protection, obtain FDA and other regulatory approvals and begin commercial sales of their products before us.

***Competitors could develop and/or gain FDA approval of our product candidates for a different indication.***

Since we do not have composition of matter patent claims for flupirtine and estriol, others may obtain approvals for other uses of these products that are not covered by our issued or pending patents. For example, the active ingredients in both Effirma (flurpirtine) and Trimesta (oral estriol) have been approved for marketing in overseas countries for different uses. Other companies, including the original developers or licensees or affiliates may seek to develop Effirma or Trimesta or their respective active ingredient(s) for other uses in the U.S. or any country we are seeking approval for. We cannot provide any assurances that any other company may obtain FDA approval for products that contain flupirtine and estriol in various formulations or delivery systems that might adversely affect our ability or the ability of Meda to develop and market these products in the U.S. We are aware that other companies have intellectual property protection using the active ingredients and have conducted clinical trials of flupirtine and estriol for different applications than what we are developing. Many of these companies may have more resources than us. We cannot provide any assurances that our products will be FDA-approved prior to our competitors.

If a product containing our active ingredients is already marketed or if the FDA approves other products containing our active ingredients in the future to treat indications, physicians may elect to prescribe and substitute a competitor's products to treat the diseases for which we are intending to commercialize; this is commonly referred to as "off-label" use. While under FDA regulations a competitor is not allowed to promote off-label uses of its product, the FDA does not regulate the practice of medicine and, as a result, cannot direct physicians to select certain products for their patients. Consequently, we might be limited in our ability to prevent off-label use of a competitor's product to treat the diseases we are intending to commercialize, even if we have issued method of use patents for that indication. If we are not able to obtain and enforce our patents, if any, or otherwise receive orphan drug protection in the case of ALS, a

competitor could develop and commercialize similar products for the same indications that we are pursuing. We cannot provide any assurances that a competitor will not obtain FDA approval for a product that contains the same active ingredients as our products.

***We rely on method patents and patent applications and various regulatory exclusivities to protect some of our product candidates and our ability to compete may be limited or eliminated if we are not able to protect our products.***

Our competitiveness may be adversely affected if we are unable to protect our proprietary technologies. We do not have composition of matter patents for Trimesta or Effirma, or their respective active ingredients estriol and flupirtine. We rely on issued patent and pending patent applications for use of Trimesta to treat MS (issued U.S. Patent Nos. 6,936,599 and 8,372,826) and various other therapeutic indications, which have been exclusively licensed to us. We have exclusively licensed an issued patent for the treatment of fibromyalgia with flupirtine, which we have sublicensed to Meda AB.

Our AEN-100 drug candidate (gastroretentive zinc acetate) is the subject of U.S. and international pending patent applications, such as published U.S. patent application Ser. No. 11/621,962 and corresponding international applications that claim priority to January 10, 2006 as well as additional patent applications. On October 26, 2011, we received a final rejection letter with regard to U.S. patent application Ser. No. 11/621,962. On February 15, 2012, we filed a Request for Continued Examination. Our inability to obtain patent protection could hinder our partnering efforts.

The patent positions of pharmaceutical companies are uncertain and may involve complex legal and factual questions. We may incur significant expense in protecting our intellectual property and defending or assessing claims with respect to intellectual property owned by others. Any patent or other infringement litigation by or against us could cause us to incur significant expense and divert the attention of our management.

