OSCIENT PHARMACEUTICALS CORP
Form 10-K
March 16, 2005
**Table of Contents**

# SECURITIES AND EXCHANGE COMMISSION

**Washington, D.C. 20549**

# FORM 10-K

**(Mark one)**

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended: December 31, 2004**

**OR**

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**Commission file number: 0-10824**

# OSCIENT PHARMACEUTICALS CORPORATION

**(Exact name of registrant as specified in its charter)**

| **Massachusetts** | **04-2297484** |
|---|---|
| **(State or other jurisdiction** | **(IRS employer** |

| of incorporation or organization) | identification number) |
|---|---|
| **1000 Winter Street Suite 2200, Waltham, Massachusetts**<br>**(Address of principal executive offices)** | **02451**<br>**(Zip Code)** |

**Registrant s telephone number: (781) 398-2300**

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**Securities registered pursuant to Section 12(b) of the Act:**

**None**

**Securities registered pursuant to Section 12(g) of the Act:**

**Common Stock, $.10 Par Value**

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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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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 an accelerated filer (as defined in Exchange Act Rule 12b-2). Yes x No ¨

The aggregate market value of the voting and non-voting common equity held by non-affiliates as of June 26, 2004, the last business day of the registrant s most recently completed second fiscal quarter, was approximately $329,200,000.

The number of shares outstanding of the registrant s common stock as of March 10, 2005 was 76,383,155.

Documents Incorporated By Reference. Portions of the registrant s proxy statement for use at its Annual Meeting to be held May 25, 2005 incorporated by reference into Part III.

Table of Contents

**Oscient Pharmaceuticals Corporation**

**ANNUAL REPORT**

**ON FORM 10-K**

**INDEX**


| | | PAGE |
|---|---|---|
| PART I | | |
| Item 1. | Business | 3 |
| Item 2. | Properties | 17 |
| Item 3. | Legal Proceedings | 17 |
| Item 4. | Submission of Matters to a Vote of Security Holders | 17 |
| PART II | | |
| Item 5. | Market for Registrant s Common Stock and Related Security Holder Matters | 18 |
| Item 6. | Selected Consolidated Financial Data | 18 |
| Item 7. | Management s Discussion and Analysis of Financial Condition and Results of Operations | 19 |
| Item 7A. | Quantitative and Qualitative Disclosures About Market Risk | 47 |
| Item 8. | Financial Statements and Supplementary Data | 48 |
| Item 9. | Changes in and Disagreements with Accountants on Accounting and Financial Disclosure | 48 |
| Item 9A. | Controls and Procedures | 48 |
| Item 9B. | Other Information | 50 |
| PART III | | |
| Item 10. | Directors and Executive Officers of the Registrant | 51 |
| Item 11. | Executive Compensation | 51 |
| Item 12. | Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters | 51 |
| Item 13. | Certain Relationships and Related Transactions | 52 |
| Item 14. | Principal Accountant Fees and Services | 52 |
| PART IV | | |
| Item 15. | Exhibits, Financial Statement Schedules and Reports on Form 8-K | 53 |
| SIGNATURES | | 57 |

Table of Contents

**PART I**

*This annual report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause the results of Oscient Pharmaceuticals to differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including any projections of revenue, expenses, earnings or losses from operations, or other financial items; any statements of the plans, strategies and objectives of management for future operations; any statements concerning product research, development and commercialization timelines; any statements of expectation or belief; and any statements of assumptions underlying any of the foregoing. The risks, uncertainties and assumptions referred to above include risks that are described under the heading Risk Factors in Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere in this annual report and that are otherwise described from time to time in our Securities and Exchange Commission reports filed after this report.*

*The forward-looking statements included in this annual report represent our estimates as of the date of this annual report. We specifically disclaim any obligation to update these forward-looking statements in the future. These forward-looking statements should not be relied upon as representing our estimates or views as of any date subsequent to the date of this annual report.*

**Item 1.** ***Business***

**Overview**

We are a biopharmaceutical company committed to the clinical development and commercialization of new therapeutics to serve unmet medical needs. We are currently a commercial-stage biopharmaceutical company focused on expanding our business in the primary care physician marketplace in the United States. In September of 2004, we launched our first product, the fluoroquinolone antibiotic FACTIVE® (gemifloxacin mesylate) tablets. Additionally, we have two product candidates for the hospital marketplace in the United States currently in development.

The Company s lead product, marketed in primary care, is the fluoroquinolone antibiotic FACTIVE (gemifloxacin mesylate) tablets, FDA-approved for the treatment of community-acquired pneumonia of mild-to-moderate severity (CAP) and acute bacterial exacerbations of chronic bronchitis (AECB). The commercial sale of FACTIVE began in September 2004. FACTIVE is also being studied in a Phase III study to explore shorter duration therapy for CAP and we are in discussions with the FDA regarding an additional indication acute bacterial sinusitis (ABS) for FACTIVE.

Our hospital product portfolio includes a novel antibiotic candidate, Ramoplanin, which is currently in clinical development for the treatment of a serious hospital-acquired infection. Ramoplanin has been studied in a Phase II trial for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) and we are currently in discussions with the FDA in connection with a special protocol assessment for the design of a Phase III program for the indication. Additionally, we have an intravenous formulation of FACTIVE in development, intended for use in hospitalized patients with pneumonia.

On February 6, 2004, we announced the completion of our merger with GeneSoft Pharmaceuticals, Inc. (Genesoft), a privately-held, pharmaceutical company based in South San Francisco, California pursuant to which, among other things, we acquired the rights to commercialize FACTIVE. Following that merger, we renamed the Company, from Genome Therapeutics to Oscient Pharmaceuticals, and began

focusing on the development and commercialization of our own products. We retain a number of pre-clinical assets based on the prior business strategies of both Genome Therapeutics and Genesoft Pharmaceuticals. These include an oral peptide deformylase inhibitor series for the potential treatment of respiratory tract infections. We also have rights to potential future milestone and royalty payments under several pharmaceutical alliances focused on the development of novel therapeutics and diagnostics for chronic human diseases and certain infectious diseases.

Table of Contents

**Business Strategy**

Our goal is to become a leading biopharmaceutical company focused on the clinical development and commercialization of new therapeutics. The key elements of our strategy to achieve this goal are as follows:

*Expanded Marketing and Further Development of FACTIVE Tablets*

Our primary business focus is the commercialization of FACTIVE in the U.S. for treating community-acquired pneumonia of mild to moderate severity and acute bacterial exacerbations of chronic bronchitis. We have built a sales and marketing infrastructure focused on the primary care physician marketplace to support commercialization and plan to pursue additional indications for FACTIVE, as well as new formulations of the product.

*Building our Primary Care Business Through New Products*

We will continue to explore ways of expanding our primary care commercial offerings and product portfolio through the co-promotion, licensing or acquisition of complementary products and product candidates.

*Building a Hospital Business  Clinical Development of Ramoplanin and intravenous FACTIVE*

Our lead product candidate is our novel antibiotic, Ramoplanin. We are advancing the clinical program of Ramoplanin toward a Phase III trial for the treatment of *Clostridium difficile*-associated diarrhea. The intravenous form of FACTIVE, for use in hospitalized patients, is also in development.

*Capturing Value in Legacy Assets*

We are exploring avenues for capturing value in our preclinical oral peptide deformylase inhibitor compounds, most likely through a partner. We also continue to monitor the progress of our pharmaceutical alliance partners and explore the possibility of selling intellectual property retained from the prior businesses of Genome Therapeutics and Genesoft Pharmaceuticals.

**Pharmaceutical Programs**

We have three ongoing product programs. Our lead program is FACTIVE oral tablets, for which we are seeking to supplement our current FDA approved claims by pursuing additional indications and treatment regimens. Our portfolio also includes Ramoplanin, a novel antibiotic in

clinical development for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) and the intravenous form of FACTIVE.

Our preclinical legacy assets include an oral peptide deformylase inhibitor series retained from Genesoft Pharmaceuticals and the rights to potential future milestone and royalty payments under five alliances based on the prior genomics discovery business of Genome Therapeutics (a summary of the biopharmaceutical alliances is included in the MD&A).

*Infectious Diseases Market*

Infectious diseases represent the second leading cause of death worldwide accounting for over 14 million deaths each year. Bacterial infections are the sixth leading cause of death in the U.S. Antibacterials represent the largest segment of the anti-infective market, with an estimated $27 billion in total worldwide sales.

The principal structural classes of antibiotics include beta-lactams, fluoroquinolones, macrolides, tetracyclines, aminoglycosides, glycopeptides and trimethoprim combinations. Penicillin, a member of the beta-lactam class, which also includes extended-spectrum penicillins, cephalosporins and carbapenems, was first developed in the 1940s. Nalidixic acid, the earliest member of the fluoroquinolone class, was discovered in the

**Table of Contents**

1960s. Major advances were made in the 1970s with the development of new beta-lactams and in the 1980s with the development of new fluoroquinolones and macrolides.

Bacterial resistance to existing antibiotics has been increasing in recent years, leading to bacterial infection recurrences, treatment failures and higher costs. These factors have fueled a growing need for more effective products in existing antibiotic classes, as well as for products with new mechanisms of action.

*Community-Acquired Respiratory Tract Infections (FACTIVE Tablets)*

*Acute Bacterial Exacerbations of Chronic Bronchitis*: Chronic bronchitis is a health problem associated with significant morbidity and mortality. It is estimated that chronic bronchitis affects up to 13 million individuals or approximately 4% to 6% of adults in the United States. Patients with chronic bronchitis are prone to frequent exacerbations, characterized by increased cough and other symptoms of respiratory distress. Longitudinal studies have estimated that 1 to 4 exacerbations occur each year in patients with chronic bronchitis, and such exacerbations are estimated to account for approximately 12 million physician visits per year in the U.S. Antibiotic therapy, the standard treatment for acute bacterial exacerbations of chronic bronchitis, or AECB, is typically effective in reducing the course of illness for patients.

*Community-Acquired Pneumonia*: Community-acquired pneumonia, or CAP, is a common and serious illness in the United States. The 3 to 4 million reported cases per year of CAP result in approximately 10 million physician visits, 1 million hospitalizations, approximately 64 million days of restricted activity and 45,000 deaths annually. Antibiotics are the mainstay of treatment for most patients with pneumonia, and where possible, antibiotic treatment should be specific to the pathogen responsible for the infection and individualized. However, since the responsible pathogen is not identified in a high proportion of patients with CAP, physicians usually take an empiric approach to treatment in the first instances. Over the last decade, resistance to penicillin and macrolides has increased significantly, and in many cases, fluoroquinolones are now recommended as a first line of therapy due to their efficacy against a wide range of respiratory pathogens, including many antibiotic resistant strains. The most recent treatment guidelines from the Infectious Diseases Society of America recommend fluoroquinolones as a first line treatment for certain higher-risk patients with CAP.

*FACTIVE Tablets*

We have the marketing rights for gemifloxacin in North America and most of Europe under the brand name FACTIVE (gemifloxacin mesylate) tablets. Gemifloxacin is a member of the fluoroquinolone class of antibiotics. In April 2003, FACTIVE was approved by the FDA for the treatment of AECB and CAP of mild to moderate severity. In July 2003, FACTIVE was also approved by the FDA to treat CAP caused by multi-drug resistant *Streptococcus pneumoniae*, or *S. pneumoniae*, a growing clinical concern. Multi-drug resistant *S. pneumoniae*, or MDRSP, is defined as *S. pneumoniae* resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins (such as cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole. FACTIVE was the first antimicrobial approved for this indication. In April of 2004, FACTIVE received marketing approval in Canada for the treatment of AECB.

FACTIVE has potent *in vitro* activity against a wide range of Gram-positive, Gram-negative and atypical pathogens, including key respiratory pathogens, such as *S. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.* FACTIVE is bactericidal at clinically achievable concentrations. Gemifloxacin, the active ingredient in FACTIVE, targets two enzymes in bacteria and has minimum inhibitory concentrations, or MICs, as low as 0.03 µg/ml for *S. pneumoniae*. In clinical trials, FACTIVE was administered to 6,775 patients and had a good overall safety and tolerability profile comparable to other currently marketed antibiotics. FACTIVE has been the subject of over 200 scientific publications. Among the research published are data indicating the drug s ability to reduce the number of AECB recurrences over a six-month period

following treatment.

Within the antibiotic market, fluoroquinolones, a product class with close to $3 billion in annual sales in the U.S. in 2004, have been gaining market share at the expense of older antibiotics, according to NDC Health. This

Table of Contents

is a trend that is expected to continue as resistance to older antibiotic classes increases. Due to its microbiological activity and clinical efficacy, FACTIVE represents an alternative choice for the treatment of certain respiratory tract infections.

*Mechanism of Action*: FACTIVE tablets act by inhibiting bacterial DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV, two enzymes essential for bacterial growth and survival. Strains of *S. pneumoniae* showing mutations in both DNA gyrase and topoisomerase IV (double mutants) are resistant to most fluoroquinolones. Since gemifloxacin has the ability to inhibit both target enzymes at therapeutically relevant drug levels, some of these *S. pneumoniae* double mutants remain susceptible to FACTIVE. FACTIVE is also active against many strains of *S. pneumoniae* that are resistant to other classes of antibiotics. There is no known bacterial cross-resistance between gemifloxacin and any other class of antimicrobials.

*Clinical Efficacy*: The clinical program for FACTIVE included 14 Phase III trials in respiratory tract infections. FACTIVE was studied for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal, double-blind, randomized, active-controlled clinical trials using 320 mg once daily for 5 days. In these non-inferiority studies, a total of 826 patients received treatment with FACTIVE tablets and 822 patients received treatment with an active comparator, namely levofloxacin, clarithromycin or amoxicillin/clavulanate. The primary endpoint was clinical response at follow-up. The results for the principal Phase III AECB studies demonstrated that FACTIVE given once daily for 5 days was at least as effective as the comparators given for 7 days. The clinical success rates for each of these three trials were as follows:

| | |
|---|---|
| FACTIVE tablets 5 days (320 mg): 88.2% | Levofloxacin 7 days (500 mg): 85.1% |
| FACTIVE tablets 5 days (320 mg): 86.0% | Clarithromycin 7 days (500 mg 2 times/day, or bid): 84.8% |
| FACTIVE tablets 5 days (320 mg): 93.6% | Amoxicillin/clavulanate 7 days (500 mg/125 mg, 3 times/day, or tid): 93.2% |

FACTIVE was also studied for the treatment of community-acquired pneumonia (CAP) in three double-blind, randomized, active-controlled clinical studies, one open, active-controlled study, and two uncontrolled studies. In total, 1,349 patients with CAP were treated with FACTIVE, including 1,037 patients treated for 7 days, while 927 patients were treated with an active comparator. The primary endpoint for each of these three trials was clinical response at follow-up.

The results of these studies showed that gemifloxacin was effective in the treatment of mild to moderate CAP. The clinical success rates for FACTIVE in studies with a fixed 7-day duration ranged from 89% to 92%. In the pivotal CAP comparator study, a 7-day treatment regimen of FACTIVE tablets 320 mg once daily was shown to be as effective as a 10-day treatment course of amoxicillin/clavulanate (500 mg/125 mg tid). The clinical success rates for the two treatment arms were:

| | |
|---|---|
| FACTIVE tablets 7 days (320 mg): 88.7% | Amoxicillin/clavulanate 10 days (500 mg/125 mg tid): 87.6% |

Clinical studies showed that FACTIVE was effective in the treatment of CAP due to penicillin-resistant *S. pneumoniae*, or PRSP. Of 11 patients with PRSP treated with FACTIVE for 7 days, 100% achieved both clinical and bacteriological success at follow-up. FACTIVE is also effective in the treatment of CAP due to MDRSP. In clinical trials, of 22 patients with MDRSP treated with FACTIVE for 7 days, 19 (87%) achieved both clinical and bacteriological success at follow-up. FACTIVE was the first antibiotic approved to treat mild to moderate CAP caused by this multi-drug resistant organism.

*Competitive Advantages*: We believe the competitive advantages of FACTIVE tablets include:

FACTIVE has been shown in *in vitro* studies to be active against many bacterial isolates resistant to other classes of antibiotics, and was the first antibiotic approved to treat community-acquired pneumonia of mild to moderate severity caused by multi-drug resistant *S. pneumoniae.*

Table of Contents

FACTIVE has a dual mechanism of action in bacteria, targeting two enzymes essential for bacterial growth and survival at therapeutically relevant drug levels, and as a result we believe has low *in vitro* potential for resistance generation.

FACTIVE can be dosed once daily, with short courses of therapy for both AECB (5 days) and CAP (7 days).

FACTIVE has patent protection into 2019, longer than any currently marketed fluoroquinolone or other antibiotic widely used to treat respiratory tract infections.

*Safety and Tolerability*: FACTIVE tablets were studied in nearly 7,000 patients in clinical trials and we estimate that to date, over 100,000 patients have taken FACTIVE since launch. In clinical trials, the incidence of adverse events reported for FACTIVE tablets was low and comparable to comparator drugs, namely beta-lactam antibiotics, macrolides and other fluoroquinolones. Most adverse events were described as mild to moderate. The most common adverse events reported in FACTIVE clinical trials were diarrhea, rash and nausea. In clinical trials, rash was reported in 2.8% of patients receiving gemifloxacin and was more commonly observed in patients less than 40 years of age, especially females. Since the launch of the drug, the adverse events reported have been consistent with those observed in the clinical development program, and with the fluoroquinolone class as a whole.

As a post-marketing commitment to the FDA, we are conducting a Phase IV trial of FACTIVE. This prospective, randomized study is comparing FACTIVE tablets (5,000 patients) to an active comparator (2,500 patients) in patients with CAP or AECB. This study includes patients of different ethnicities so that we can ascertain safety information in populations not substantially represented in the existing clinical trial program, specifically as it relates to rash. Patients will be evaluated for clinical and microbiological success. This Phase IV trial was initiated in the fall of 2004 with expected completion within three to four years.

*Additional Development of Gemifloxacin:* Clinical trials of FACTIVE for the treatment of acute bacterial sinusitis, or ABS, have also been completed. Two double-blind, randomized, active-controlled clinical studies were conducted to examine the efficacy of FACTIVE 320 mg once daily for 7 days in the treatment of patients with ABS. In these studies, 540 patients received FACTIVE tablets and 536 patients received active comparator, namely trovafloxacin or cefuroxime. The primary endpoint was clinical success at follow-up. The result of these clinical trials showed comparable clinical success for patients treated with FACTIVE tablets and those treated with comparator drugs. In addition, a double-blind, randomized, active-controlled clinical study comparing a FACTIVE 7-day treatment regimen for ABS with a FACTIVE 5-day treatment regimen showed similar efficacy between the two treatment arms. Three open-label studies also support the efficacy of FACTIVE tablets given for 5 days for the treatment of ABS. It is our belief that all necessary clinical trials are complete and that the gathering of additional data from the post-marketing experience of the drug will supplement our NDA filing although how long or how much data will be required is not yet determined. We are in discussions with the FDA concerning the regulatory requirements for potential submission of a New Drug Application (NDA) for this indication in 2005.

We are also developing an intravenous formulation of gemifloxacin. We expect that FACTIVE intravenous will need to undergo a Phase I bioequivalence study plus, pending a successful outcome of the first study, we believe a single Phase III trial of the intravenous formulation would be required before seeking marketing approval from the FDA.

*License Agreement*: We license the rights to gemifloxacin, the active ingredient in FACTIVE tablets, from LG Life Sciences of the Republic of Korea. We have the rights to commercialize gemifloxacin in North America, France, Germany, the United Kingdom, Luxembourg, Ireland, Italy, Spain, Portugal, Belgium, the Netherlands, Austria, Greece, Sweden, Denmark, Finland, Norway, Iceland, Switzerland, Andorra, Monaco, San Marino and Vatican City. The term of the agreement extends at least through the patent life of the compound which currently expires in 2018 with respect to the principal composition of matter patents for gemifloxacin, and the term could

7

Table of Contents

extend further depending upon several factors, including whether we obtain patent extensions and the timing of our commercial sale of the product in a particular country. The agreement also requires achievement of a minimum level of sales commitment over a period of time, which if not met, would result in the product being returned to LG Life Sciences. Under this agreement, we are responsible, at our expense and through consultation with LG Life Sciences, for the clinical and commercial development of gemifloxacin in the countries covered by the license, including the conduct of clinical trials, the filing of drug approval applications with the FDA and other applicable regulatory authorities and the marketing, distribution and sale of gemifloxacin in our territories; provided, that LG Life Sciences has the right to co-promote the product, on terms to be negotiated, in our territories beginning in 2008 and periods commencing thereafter.

Under our license agreement, we were required to pay LG Life Sciences $8 million upon the completion of the merger with Genesoft and will have to make additional payments up to $22 million when specific commercialization milestones are achieved. We are required to buy bulk drug from LG Life Sciences (see Manufacturing below), and will pay LG Life Sciences a royalty on sales in North America and the territories covered by the license in Europe.

*Hospital-Acquired Infections (Ramoplanin)*

*Clostridium difficile*-Associated Diarrhea (CDAD): CDAD, a serious form of colitis caused by toxins produced by the Gram-positive bacterium *Clostridium difficile* (*C. difficile*), is the most common form of antibiotic-associated diarrhea in the hospital setting. One study has demonstrated that as many as 20% of hospital patients are colonized with *C. difficile* either prior to or during admission. Because it is a spore-forming bacterium, *C. difficile* is readily spread from person to person, especially in the hospital and nursing home environment. Under certain conditions, such as extended antibiotic therapy and gastrointestinal surgery, *C. difficile* can colonize the gut and release toxins, leading to bowel inflammation and severe diarrhea. Serious cases can occur and involve the development of fulminant colitis (severe inflammation of the colon); such occurrences can be life threatening, especially in elderly or immunocompromised populations.

Over 400,000 patients are treated in U.S. hospitals each year for CDAD. CDAD is associated with an average increase of length of stay in the hospital of 3.6 days and an average increase in hospital costs of over $3,600 per patient. It is estimated that the annual increase in hospital costs attributable to CDAD exceeds $1 billion.

Current therapies for the treatment of CDAD include oral metronidazole and oral vancomycin. Both of these agents are associated with a 15-20% relapse rate. The use of oral vancomycin has been associated with the emergence of vancomycin-resistant organisms, including vancomycin-resistant enterococci (VRE). Resistance has also been reported for metronidazole.

*Ramoplanin*

In October 2001, we in-licensed Ramoplanin from Vicuron Pharmaceuticals Inc. (Vicuron). Ramoplanin is a novel glycolipodepsipeptide antibiotic produced by fermentation of the bacteria *Actinoplanes*, with activity against Gram-positive aerobic and anaerobic microorganisms. In preclinical studies, Ramoplanin has been shown to be bactericidal against most Gram-positive species, including methicillin-resistant staphylococci, VRE and *C. difficile*. Ramoplanin inhibits the bacterial cell wall peptidoglycan biosynthesis with a mechanism different from that of vancomycin, teicoplanin or other cell wall-synthesis inhibitors. No evidence of cross-resistance between Ramoplanin and other glycopeptide antibiotics has been observed. Ramoplanin has a unique profile that may make it a particularly attractive compound for killing bacteria in the GI tract. As a result, we are studying the product candidate for the treatment of infections caused by *C. difficile* that occur in the GI tract.

*Clinical Trials*: In July of 2004, we completed our Phase II trial to assess the safety and efficacy of Ramoplanin in the treatment of CDAD. The open-label study enrolled 87 people in 24 U.S. sites. The trial

Table of Contents

compared two doses of Ramoplanin (200 mg and 400 mg twice daily) to vancomycin (which requires a dose of 125 mg four times daily for the treatment of CDAD). Both agents were administered for ten days, during which data on Ramoplanin was collected to measure safety and efficacy. The primary endpoint of the study was response rate at the test-of-cure visit, 7-14 days post-therapy. For this trial, the response rates were 60% for Ramoplanin 200 mg, 71% for Ramoplanin 400 mg, and 78% for vancomycin 125 mg in the clinically evaluable population. A potentially more clinically relevant endpoint, response at the end of therapy, was also assessed. At the end of therapy, the response rates were 83% for Ramoplanin 200 mg, 85% for Ramoplanin 400 mg and 86% for vancomycin 125 mg. We have submitted a special protocol assessment (SPA) to the FDA for the Phase III program of Ramoplanin for CDAD. These Phase II results are being discussed with the FDA as part of our SPA submission. Pending a successful outcome of these discussions and successful timetable discussions with our partner, Vicuron, the program would be ready to initiate the Phase III trial. Ramoplanin has demonstrated both *in vitro* and *in vivo* (hamster model) activity against *C. difficile,* including strains resistant to metronidazole and vancomycin. The clinical development program of Ramoplanin for the potential treatment of CDAD received Fast Track status from the FDA in February 2004.

Previously, Ramoplanin was studied in a Phase II, multicenter, double-blind, placebo-controlled trial examining suppression of GI VRE colonization. In that study, Ramoplanin was well tolerated. After seven days of treatment, 90% of patients who were colonized with VRE at the beginning of the study had no detectable VRE in their GI tract, while all of the placebo patients had detectable VRE (p=0.01). Ramoplanin was also studied in a Phase III trial for the prevention of bloodstream infections caused by vancomycin-resistant enterococci. That studied was closed prior to completion, due to slow enrollment, and we expect to use the data from the study as part of a safety database for Ramoplanin. Additionally, we conducted a Phase I study of Ramoplanin for the potential control of VRE transmission in the hospital-setting.

*Potential Competitive Advantages*: The potential competitive advantages of Ramoplanin are:

- Ramoplanin is from a novel class of antibiotics and there have been no observed cases of bacterial resistance or cross-resistance with other antibiotics.
- Ramoplanin is orally administered, but not absorbed into the bloodstream, so it concentrates and exerts its killing effects in the GI tract.
- Its bactericidal effect may result in lower potential for bacteria to develop resistance.
- Ramoplanin has a Gram-positive spectrum of activity and low potency against Gram-negative anaerobes that normally colonize the GI tract making it less likely that its use will result in the overgrowth of other opportunistic organisms.

*License Agreement*: Our license agreement with Vicuron provides us with exclusive rights to develop and market oral Ramoplanin in the U.S. and Canada. Under this agreement, we are responsible, at our expense, for the clinical and non-clinical development of Ramoplanin in our field, the prevention and treatment of human disease, in the United States and Canada, including the conduct of clinical trials and the filing of drug approval applications with the FDA and other applicable regulatory authorities. Vicuron is responsible for providing us with all information in its possession relating to Ramoplanin in our licensed field and for cooperating with us in obtaining regulatory approvals of Ramoplanin. We are obligated to purchase and Vicuron is obligated to provide the bulk material for the manufacture of the product. Under the terms of the agreement, we paid Vicuron initial consideration of $2 million. We will also make milestone payments of up to an additional $8 million in a combination of cash and notes convertible into our stock if certain development milestones are met. In addition to purchasing bulk active pharmaceutical ingredients from Vicuron, we will pay a royalty to Vicuron on product sales. The combined total of bulk product purchases and royalties is expected to be 26% of our net product sales. Pursuant to the terms of our amended agreement with Vicuron, we and Vicuron are in discussions to develop a timetable for the development of Ramoplanin to determine an outside date for the filing of an NDA.

9

Table of Contents

**Legacy Genomics-Based Drug Discovery Alliances**

In the past, it was our business strategy to form strategic alliances with major pharmaceutical companies to discover, develop and commercialize products based on our gene discoveries. While we have shifted our focus away from forming alliances of this type and have discontinued our gene discovery activities, our existing pharmaceutical alliances still have the potential to deliver value in the future. We believe these programs (a summary of these programs is included in the MD&A) all to be in the preclinical stage of development.

**Internal Drug Discovery**

*Bacterial Infections*

Our current portfolio of internal drug discovery programs focuses on bacterial infections and the growing need to develop antibacterial compounds with novel mechanisms of action.

*Peptide Deformylase Inhibitors*: In August 2002, Genesoft entered into a research and license agreement with British Biotech Pharmaceuticals Ltd., now Vernalis, to co-develop inhibitors of peptide deformylase, or PDF, a novel iron-binding enzyme essential for bacterial growth but not involved in human cytoplasmic protein synthesis. We believe that PDF inhibitors represent an excellent opportunity for the development of novel mode of action antibiotics.

Preclinical studies of our first-generation PDF inhibitor indicated that the compound may have potential for the treatment of hospitalized patients suffering from CAP. An intravenous formulation of this compound entered Phase I clinical trials in October 2002. The drug candidate was well tolerated and demonstrated good pharmacokinetic properties, but did not have an ideal spectrum of activity against common respiratory pathogens. The next step is to focus on the optimization of second-generation, orally-available PDF inhibitors with the potential to target the broader community-based antibiotic market. Several compounds have been identified with improved properties, including good activity against *H. influenzae.* Continued success of this program is contingent on securing a development partnership with another organization.

**Discontinuation of Genomics Services Business**

As part of our continued evolution into a focused biopharmaceutical company, in March 2003 we sold our genomics services business to privately held Agencourt Bioscience Corporation (Agencourt). As part of the agreement, we transferred our sequencing operations, including certain equipment and personnel to Agencourt. We received an upfront cash payment of $200,000 and shares of Agencourt common stock and we will receive a percentage of revenues from commercial and government customers that were transferred to Agencourt for a period of two years from the date of the agreement. As of December 31, 2004, we have received approximately $792,000 in royalties.

The PathoGenome Database, a database consisting of proprietary and publicly available genetic information from over thirty microbial organisms, including organisms responsible for the most prevalent bacterial infections has, since 2001, been marketed, maintained and distributed by EraGen Biosciences. We retain our rights to use it and receive a percentage of subscription fees and royalties for approximately

$181,000 from subscriber discoveries, and we do not expect that this program will have a significant impact on our business moving forward.

**Patents and Proprietary Technology**

Our commercial success depends in part on our ability to obtain intellectual property protection on our methods, technologies and discoveries. To that end, our policy is to protect our proprietary technology primarily through patents.

We currently own or license approximately 63 issued U.S. patents, approximately 84 pending U.S. patent applications, 113 issued foreign patents and approximately 198 pending foreign patent applications. These

Table of Contents

patents and patent applications primarily relate to (1) the field of human and pathogen genetics, (2) the chemical composition, use, and method of manufacturing FACTIVE tablets, (3) metalloenzyme inhibitors, their uses, and their targets, and (4) DNA-Nanobinder compounds and their use as anti-infective therapeutics. Our material patents are as follows:

U.S. Patent No. 5,633,262 granted May 27, 1997, relating to quinoline carboxylic acid derivatives having 7-(4-amino-methyl-3-oxime) pyrrolidine substituent; licensed from LG Life Sciences; expiring June 15, 2015;

U.S. Patent No. 5,776,944 granted July 7, 1998, relating to 7-(4-aminomethyl-3-methyloxyiminopyrroplidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015;

U.S. Patent No. 5,869,670 granted February 9, 1999, relating to 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015;

U.S. Patent No. 5,962,468 granted October 5, 1999, relating to 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015;

U.S. Patent No. 6,340,689 granted January 22, 2002, relating to methods of using quinolone compounds against atypical upper respiratory pathogenic bacteria; licensed from LG Life Sciences; expiring September 14, 2019;

U.S. Patent No. 6,262,071 granted July 17, 2001, relating to methods of using antimicrobial compounds against pathogenic Mycoplasma bacteria; licensed from LG Life Sciences; expiring September 21, 2019;

U.S. Patent No. 6,331,550 granted December 18, 2001, relating to methods of using of quinolone compounds against anaerobic pathogenic bacteria; licensed from LG Life Sciences; expiring September 21, 2019;

U.S. Patent No. 6,455,540 granted September 24, 2002, relating to methods of Use of quinolone compounds against anaerobic pathogenic bacteria; licensed from LG Life Sciences; expiring September 21, 2019;

U.S. Patent No. 6,723,734 granted April 20, 2004, relating to the salt of naphthyridine carboxylic acid derivative; licensed from LG Life Sciences, expiring March 20, 2018;

U.S. Patent No. 6,803,376 granted October 12, 2004, relating to methods of use of quinolone compounds against pneumococcal pathogenic bacteria; licensed from LG Life Sciences; expiring September 21, 2019.

We are not currently involved in any litigation, settlement negotiations, or other legal action regarding patent issues and we are not aware of any patent litigation threatened against us. Our patent position involves complex legal and factual questions, and legal standards relating to the validity and scope of claims in the applicable technology fields are still evolving. Therefore, the degree of future protection for our proprietary rights is uncertain.

Under our license agreement with LG Life Sciences, we obtained an exclusive license to develop and market gemifloxacin in certain territories. This license covers 15 issued U.S. patents and a broad portfolio of corresponding foreign patents and pending patent applications. These patents include claims that relate to the chemical composition of FACTIVE tablets, methods of manufacturing and their use for the prophylaxis and treatment of bacterial infections. The U.S. patents are currently set to expire at various dates, ranging from 2018, in the case of the principal patents relating to FACTIVE tablets, to 2019. We have filed patent term extension applications, covering the regulatory review process, for the principal patents. If granted, these extensions would

Table of Contents

extend the exclusivity period through 2017. We also have the exclusive right to use FACTIVE trademarks, trade names, domain names and logos in conjunction with the use or sale of the product in the territories covered by the license.

LG Life Sciences has the obligation under the agreement to diligently maintain its patents and the patents of third parties to which it has rights that, in each case, relate to gemifloxacin, the active ingredient in FACTIVE tablets. We have the right, at our expense, to control any litigation relating to suits brought by a third party alleging that the manufacture, use or sale of gemifloxacin in its licensed field in the territories covered by the license infringes upon our rights. We also have the primary right to pursue actions for infringement of any patent licensed from LG Life Sciences under the license agreement within the territories covered by the license. If we elect not to pursue any infringement action, LG Life Sciences has the right to pursue it. The costs of any infringement actions are first paid out of any damages recovered. If we are the plaintiff, the remainder of the damages are retained by us, subject to our royalty obligations to LG Life Sciences. If LG Life Sciences is the plaintiff, the remainder of the damages are divided evenly between us and LG Life Sciences, subject to our royalty obligations to LG Life Sciences.

We also have the exclusive right to use factive trademarks, trade names, domain names and logos in conjunction with the use or sale of the product in the territories covered by the license.

LG Life Sciences, as owner of U.S. Patent Nos. 5,776,944 and 5,962,468, submitted requests for reexamination to the U.S. Patent & Trademark Office, or PTO, in order to place additional references into the record of each patent. Both requests were granted by the PTO. Patents 944 and 468 have been reexamined with relatively minor modifications to the claims and confirmed patentable over the submitted references.

Under our agreement with Vicuron, we obtained an exclusive license to develop and market oral Ramoplanin in the United States and Canada. The patents to Ramoplanin that we licensed under our agreement with Vicuron include claims relating to methods of manufacturing Ramoplanin as well as methods increasing the yield of the active compound. We also have applications pending relating to various novel uses of Ramoplanin. The patent covering the chemical composition of Ramoplanin has expired. To provide additional protection for Ramoplanin, we rely on proprietary know-how relating to maximizing yields in the manufacture of Ramoplanin, and intend to rely on the five year data exclusivity provisions under the Hatch-Waxman Act.

Vicuron has the obligation under our agreement to prosecute patents relating to Ramoplanin that are made by Vicuron personnel or conceived jointly by our personnel and Vicuron s personnel. We have the obligation to prosecute patents relating to Ramoplanin that are made solely by our personnel. We have the right to control any suits brought by a third party alleging that the manufacture, use or sale of Ramoplanin in our licensed field in the United States or Canada infringes upon our rights. We will bear the costs of any such actions; provided that if we are obligated to pay any royalties or other payments to a third party to sell Ramoplanin as a result of this litigation, Vicuron is obligated to pay that expense. We also have the primary right to pursue actions for infringement of any patent licensed from Vicuron within the United States and Canada within our licensed field. Vicuron has the primary right to pursue actions for infringement of any patents that it licenses to us outside of our licensed field within the United States and Canada and for all purposes outside of the United States and Canada. If the party with the primary right to pursue the infringement action elects not to pursue it, the other party generally has the right to pursue it. The costs of any infringement actions are first paid out of any damages recovered and are then allocated to the parties depending upon their interest in the suit.

We have exclusively licensed rights from Vernalis for the research, development and commercialization of certain anti-infectives under Vernalis patent portfolio relating to metalloenzyme inhibitors (including peptide deformylase inhibitors), their uses and related targets.

Our own patent portfolio also comprises patents relating to DNA-nanobinder technology and their applications as anti-infective therapeutics. Certain patents and patent applications relating to DNA-nanobinder technology resulted from research funded by the U.S. government.

12

Table of Contents

We also rely upon trademarks, unpatented trade secrets and improvements, unpatented know-how and continuing technological innovation to develop and maintain our competitive position. We generally protect this information with confidentiality agreements that provide that all confidential information developed or made known to others during the course of the employment, consulting or business relationship shall be kept confidential except in specified circumstances. Agreements with employees provide that all inventions conceived by the individual while employed by us are our exclusive property. We cannot guarantee, however, that these agreements will be honored, that we will have adequate remedies for breach if they are not honored or that our trade secrets will not otherwise become known or be independently discovered by competitors.

**Competition**

FACTIVE tablets are approved for the treatment of community-acquired pneumonia of mild to moderate severity and acute bacterial exacerbations of chronic bronchitis. There are several classes of antibiotics that are primary competitors for the treatment of these indications, including:

- other fluoroquinolones such as Levaquin® (levofloxacin), a product of Ortho-McNeil Pharmaceutical, Inc., Tequin® (gatifloxacin), a product of Bristol-Myers Squibb Company, and Cipro® (ciprofloxacin) and Avelox® (moxifloxacin), both products of Bayer Corporation;

- ketolides, such as Ketek® (telithromycin), a product of Sanofi-Aventis,

- macrolides such as Biaxin® (clarithromycin), a product of Abbott Laboratories and Zithromax® (azithromycin), a product of Pfizer Inc.; and

- penicillins such as Augmentin® (amoxicillin/clavulanate potassium), a product of GlaxoSmithKline.

In addition, many generic antibiotics are also currently prescribed to treat these infections.

Ramoplanin is currently in development for the for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). We are aware of two products currently utilized in the marketplace Vancocin® (vancomycin), a product of ViroPharma, and metronidazole, a generic product for treatment of this indication. We are also aware of at least two companies with products in development for the treatment of CDAD a Genzyme compound which has completed Phase II; and an Acambis compound in Phase I. It is also possible that other companies are developing competitive products for this indication.

We are also aware that Vicuron and Novartis Pharma are jointly developing PDF inhibitor agents that may compete with any PDF products we develop.

All of our other internal product programs are in early stages and are not yet indication specific. Our alliance-related product development programs are also all in preclinical stages, and it is therefore not possible to identify any product profiles or competitors for these product development programs at this time. Our industry is very competitive and it therefore is likely that if and when product candidates from our early stage internal programs or our alliance programs reach the clinical development stage or are commercialized for sale, these products will also

face competition.

The biopharmaceutical industry generally, and our drug development programs specifically, are characterized by rapidly evolving technology and intense competition. Our competitors include pharmaceutical and biotechnology companies both in the United States and abroad. Many of our competitors have substantially greater capital resources, facilities and human resources than we do.

Competition with respect to our product and product candidates is and will be based on, among other things:

- our sales and marketing expertise,
- our clinical trial results and post marketing experience,

Table of Contents

- our ability to obtain regulatory approvals for our product candidates in a cost efficient and timely manner and subsequently remain in regulatory compliance,
- our ability to attract and retain qualified personnel,
- our ability to obtain patent protection and defend our patent challenges,
- our ability to in-license product candidates for clinical development,
- our ability to secure sufficient capital resources to fund our research, clinical development and sales and marketing operations, and
- our ability and our partners ability to develop and commercialize therapeutic, vaccine and diagnostic products based upon our discoveries.

Because we rely primarily on in-licensing and acquisitions of products and product candidates to expand our portfolio, it is important to note that we may also face increasing competition for in-licensing and acquisition opportunities from leading pharmaceutical and biotechnology companies. We cannot be certain that we will be able to in-license product opportunities in the future or acquire new products. Competitive disadvantages in any of these areas could materially harm our business and financial condition.

**Government Regulation**

Regulation by governmental entities in the United States and other countries will be a significant factor in the development, manufacturing and marketing of any product candidates that we develop or commercialize. The extent to which such regulation may apply to our collaborators or us will vary depending on the nature of the product. Virtually all of our or our collaborators pharmaceutical products will require regulatory approval by governmental agencies prior to commercialization. In particular, the FDA in the United States and similar health authorities in foreign countries subject human therapeutic and vaccine products to rigorous preclinical and clinical testing and other approval procedures. Various U.S. federal and, in some cases, state statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of human therapeutic and vaccine products. Obtaining these approvals and complying with appropriate federal and foreign statutes and regulations requires a substantial amount of time and financial resources.

The FDA regulates human therapeutic products in one of three broad categories: drugs, biologics or medical devices. Our lead product, FACTIVE tablets, has FDA marketing approval for the treatment of community-acquired pneumonia of mild severity and acute bacterial exacerbations of chronic bronchitis. Our most advanced product candidate, Ramoplanin, currently being studied for the treatment of *Clostridium difficile*-associated diarrhea, will be regulated by the Center for Drug Evaluation and Research (CDER). Products developed as a result of our genomics-based development programs could potentially fall into all three categories. The FDA generally requires the following steps for pre-market approval of a new drug or biological product:

- preclinical laboratory and animal tests,

submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical trials may begin,

adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for its intended indication,

submission to the FDA of a marketing application; a new drug application, or NDA, if the FDA classifies the product as a new drug; or a biologics license application, or BLA, if the FDA classifies the product as biologic, and

FDA review of the marketing application and NDA or BLA in order to determine, among other things, whether the product is safe and effective for its intended uses and is appropriately manufactured.

Table of Contents

Our collaborators may also develop diagnostic products based upon the human or pathogen genes that we identified. We believe that the FDA is likely to regulate these diagnostic products as devices rather than drugs or biologics. The nature of the FDA requirements applicable to diagnostic devices depends on how the FDA classifies the diagnostic devices. The FDA most likely will classify a diagnostic device that our collaborators develop as a Class III device, requiring pre-market approval. Obtaining pre-market approval involves the following process, rather like that of obtaining a BLA or a NDA, which may be costly and time-consuming:

- conducting pre-clinical studies,
- obtaining an investigational device exemption to conduct clinical tests,
- conducting clinical trials,
- filing a pre-market approval application with safety and efficacy data and manufacturing information, and
- attaining FDA approval for a specific intended use.

Products on the market are subject to continual review by the FDA. Therefore, subsequent discovery of previously unknown problems, or failure to comply with the applicable regulatory requirements may result in restricted marketing or withdrawal of the product from the market and possible civil or criminal sanctions. The FDA also may subject biologic products to batch certification and lot release requirements. There are additional regulatory requirements for products marketed outside the United States governing the conduct of clinical trials, product licensing, advertising and promotion, post-approval reports, manufacturing, pricing and reimbursement.

As a post-marketing study commitment, the FDA has required a prospective, randomized study comparing FACTIVE tablets (5,000 patients) to an active comparator (2,500 patients) in patients with CAP or AECB. This study will include patients of different ethnicities, to gain safety information in populations not substantially represented in the existing clinical trial program, specifically as it relates to rash. Patients will be evaluated for clinical and laboratory safety. This Phase IV trial is underway. The results of this trial, if unfavorable, could restrict our ability to commercialize FACTIVE tablets.

Manufacturing facilities that produce drugs, biologics or medical devices are also subject to extensive regulation both by the FDA and foreign regulatory authorities. These regulations require, among other things, that our facilities and the facilities of third parties, such as LG Life Sciences, that produce products for us, be registered with the FDA, comply with current Good Manufacturing Practices and pass periodic inspections by the FDA. Facilities in foreign countries may be subject to inspection by FDA, local regulators or both. Current Good Manufacturing Practices, or cGMP, require extensive recordkeeping, quality control, documentation and auditing to ensure that products meet applicable specifications. Failure to comply with these requirements can result in warning letters, requirements of remedial action, and, in the case of more serious failures, suspension of manufacturing, seizure or recall of product and fines and penalties. Compliance with these requirements can be time consuming, costly and can result in delays in product approval or product sales.

**Sales and Marketing**

We have rights to market FACTIVE tablets in North America and parts of Europe.

We are selling FACTIVE through our own sales and marketing organization in the U.S. Our sales representatives, currently contracted through Publicis Selling Solutions (PSS), focus on high-prescribing primary care physicians and opinion leaders who represent about 40% of the total respiratory tract infection prescription universe. We intend to seek a co-promotion partner in the U.S. to broaden our marketing efforts. We have also built a team of professionals with experience in medical education, insurance and government reimbursement, medical affairs, marketing, advertising and scientific communications.

Table of Contents

We believe that the commercial success of FACTIVE tablets, especially in territories outside of the U.S., will benefit from the additional resources that a pharmaceutical marketing partner would provide. We anticipate that we will rely upon a co-promotion partner in our licensed territories in Europe and Canada to facilitate the filing of required regulatory submissions, to assist with necessary reimbursement discussions and to help us market and sell the product in those territories.

We also have the exclusive right to market Ramoplanin in the U.S. and Canada, if approved by regulatory authorities.

**Manufacturing**

In October 2002, Genesoft, now our subsidiary, entered into a license and option agreement with LG Life Sciences to develop and commercialize gemifloxacin, a novel quinolone antibiotic, in North America, France, Germany, the United Kingdom, Luxembourg, Ireland, Italy, Spain, Portugal, Belgium, the Netherlands, Austria, Greece, Sweden, Denmark, Finland, Norway, Iceland, Switzerland, Andorra, Monaco, San Marino and Vatican City. The term of the agreement with respect to each country extends at least through the life of the patents covering gemifloxacin in such country. In the United States, the last of the currently issued patents expires in 2019. The product was approved for sale in the United States in April 2003 for the treatment of acute bacterial exacerbation of chronic bronchitis and community-acquired pneumonia of mild to moderate severity.

Under the terms of the agreement, LG Life Sciences has agreed to supply and we are obligated to purchase from LG Life Sciences all of the Company s anticipated commercial requirements for FACTIVE bulk drug. LG Life Sciences is expected to supply the FACTIVE bulk drug substance from its manufacturing facility in South Korea. We have initiated a technology transfer process with Patheon Inc. for the manufacture of finished products, to replace the previous fill and finish provider, SB Pharmco. We estimate that Patheon will obtain the necessary FDA qualifications to be the fill and finish provider of FACTIVE tablets during the first half of 2005. We expect that the quantities of FACTIVE tablets currently on hand, in combination with the quantities to be delivered from SB Pharmco, pursuant to pending purchase orders, will provide us with sufficient inventory until Patheon can be qualified. Assuming success on ongoing testing on the validation batches of FACTIVE tablets prepared by Patheon, these validation batches and additional inventory of tablets at Patheon are expected to be available for commercial use during the second quarter of 2005.

The terms of our agreement for Ramoplanin obligate the licensor, Vicuron, to manufacture the bulk drug. We are responsible for the manufacture of the finished dosage form for the United States and Canada. We currently use a contract manufacturer to produce Ramoplanin for our clinical trial program and would also plan to use a contract manufacturer to produce the final dosage to support commercial sales. In the event we decide to establish a manufacturing facility of our own, we will require substantial additional funds and will need to hire and train significant additional personnel and will need to comply with the cGMP.

**Human Resources**

As of December 31, 2004, we had 94 full-time equivalent employees, with 20 of these employees engaged in clinical development, 42 of them conducting sales and marketing functions and 32 providing general and administrative capabilities. Three of our employees held M.D.s and 26 more held other advanced degrees including MBAs, Juris Doctors or equivalent degrees. In addition, we had 171 sales representatives in our contract sales force. It is expected that our sales force will change from contract status to full-time employee status sometime in 2005. This agreement affords us the flexibility to hire, train and manage a large sales force and to evaluate talent over time. We met