PHARMION CORP
Form 10-K
March 26, 2004

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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

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

for the fiscal year ended December 31, 2003.

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

For the transition period from to .

Commission file number 000-50447

Pharmion Corporation

(Exact name of Registrant as specified in its charter)

Delaware	**84-1521333**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*

2525 28th Street, Suite 200
Boulder, Colorado 80301
(720) 564-9100
(Address, including zip code, and telephone number, including area code, of principal executive offices)

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

None

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

Common Stock $.001 Par Value
(Title of Class)

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 þ No o

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

Indicate by check mark whether the Registrant is an accelerated filer (as defined by Exchange Act Rule 12b-2). Yes o No þ

There was no established public trading market for the Registrant s Common Stock as of the last business day of the Registrant s most recently completed second fiscal quarter.

As of March 25, 2004, there were 25,293,930 shares of the Registrant s Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant s definitive Proxy Statement for its 2004 Annual Meeting of Stockholders are incorporated by reference into Part III of this report on Form 10-K to the extent stated therein.

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PART I

Unless the context requires otherwise, references in this report to Pharmion, the Company, we, us, and our refer to Pharmion Corporat

All statements, trend analysis and other information contained in this Form 10-K and the information incorporated by reference which are not historical in nature are forward-looking statements within the meaning of the Private-Securities Litigation Reform Act of 1995. These forward-looking statements include, without limitation, discussion relative to markets for our products and trends in revenue, gross margins and anticipated expense levels, as well as other statements including words such as anticipate, believe, plan, estimate, expect and intend and c similar expressions. All statements regarding our expected financial position and operating results, business strategy, financing plans, forecast trends relating to our industry are forward-looking statements. These forward-looking statements are subject to business and economic risks and uncertainties, and our actual results of operations may differ materially from those contained in the forward-looking statements. Although we may elect to update forward-looking statements in the future, we specifically disclaim any obligation to do so, even if our estimates change, and readers should not rely on those forward-looking statements as representing our views as of any date subsequent to the date of this annual report.

Item 1. ***Business***
Overview

We are creating a global pharmaceutical company focused on acquiring, developing and commercializing innovative products for the treatment of hematology and oncology patients. We have established our own regulatory, development and sales and marketing organizations covering the U.S., Europe and Australia. We have also developed a distributor network to serve the hematology and oncology markets in 20 additional countries throughout the Middle East and Asia. To date, we have acquired rights to two marketed products, Innohep® and Refludan®. We also have two products, Thalidomide Pharmion 50mg and Vidaza, in registration that we believe represent significant market opportunities. With our combination of regulatory, development and commercial capabilities, we intend to continue to build a balanced portfolio of approved and pipeline products targeting the hematology and oncology markets.

Our current product portfolio consists of the following four products:

Thalidomide Pharmion 50mg (thalidomide) Thalidomide has become a standard of care for the treatment of relapsed and refractory multiple myeloma, a cancer of the plasma cells in the bone marrow. We have licensed the marketing rights to thalidomide from Celgene Corporation and Penn T Limited for all countries outside of North America and certain Asian markets. We began selling thalidomide in Europe on a compassionate use or named patient basis under a stringent risk management program in the third quarter of 2003 while we actively seek full regulatory approval for this drug in Europe and several additional countries. In the fourth quarter of 2003, Thalidomide Pharmion 50mg was approved as a treatment for relapsed and refractory multiple myeloma and erythema nodosum leprosum, or ENL, in Australia and New Zealand. These approvals were the first regulatory approval of thalidomide for the treatment of multiple myeloma anywhere in the world.

Vidaza (azacitidine) Vidaza is the subject of a completed and published Phase III study indicating its safety and efficacy in the treatment of myelodysplastic syndromes, or MDS, a bone marrow disorder characterized by the production of abnormally functioning, immature blood cells. We obtained worldwide rights to this product from Pharmacia & Upjohn Company, now a part of Pfizer, Inc. We submitted a New Drug Application, or NDA, to the Food and Drug Administration, or FDA, for Vidaza in December 2003 and anticipate making comparable filings in Europe and Australia later this year. In February 2004, the FDA accepted for filing, and granted Priority Review classification to, our Vidaza NDA. Priority Review status of the NDA reduces the standard FDA response time to six months, and targets an agency response on or before June 29, 2004. In connection with these

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submissions in the fourth quarter of 2003, we initiated a confirmatory study of Vidaza in MDS, which will be one of the largest studies in MDS to date.

Innohep® (tinzaparin) Innohep® is a low molecular weight heparin approved in the U.S. for the treatment of deep vein thrombosis, or DVT, which occurs when a blood clot develops in the deep veins of the legs. We obtained the U.S. rights to this product from LEO Pharma A/S, which markets Innohep® in Europe and several additional countries. We relaunched Innohep® as a treatment for DVT in cancer patients in the fourth quarter of 2002, and used this drug to establish our U.S. sales and marketing organization.

Refludan® (lepirudin) Refludan® is an antithrombin agent approved in the U.S., Europe and several additional countries for the treatment of heparin-induced thrombocytopenia, or HIT, an allergic, adverse immune response to heparin, resulting in an absence of sufficient cell platelets to enable blood clotting. We obtained rights to this product in all countries outside of the U.S. and Canada from Schering AG. We began selling Refludan®in Europe and Australia in the third quarter of 2002, and used this drug to establish our European and Australian sales and marketing organizations.

We were incorporated in Delaware in August 1999 and commenced operations in January 2000. Our principal executive offices are located at 2525 28th Street, Boulder, Colorado 80301, and our telephone number is (720) 564-9100. Our website is located at www.pharmion.com. The reference to our website does not constitute incorporation by reference of the information contained on our website into this annual report on Form 10-K.

Our periodic and current reports, and all amendments to those reports, are available free of charge, on our website at www.pharmion.com, as soon as reasonably practicable after we have electronically filed them with, or furnished them to, the Securities and Exchange Commission.

Our Strategy

We believe that there are significant opportunities available for a global pharmaceutical company with a focus on the hematology and oncology markets. Our strategy for taking advantage of these opportunities includes the following key elements:

Focusing on the hematology and oncology markets. We focus on the hematology and oncology markets for several reasons. The hematology and oncology markets are characterized by a number of disorders with high rates of recurrence and a limited response from current therapies or treatments, many of which include severe side effects. New hematology and oncology product candidates addressing unmet medical needs or providing a superior safety profile are frequently the subject of expedited regulatory reviews and, if approved and effective, can experience rapid adoption rates. While the overall global hematology and oncology markets are substantial, many drugs directed at hematology and oncology patients treat relatively small patient populations or subsets of patients with a specific cancer type. Because large, multinational pharmaceutical companies are increasingly seeking products with very large revenue potential, they often do not devote resources to develop drugs they discover with the potential to treat these patient populations, presenting us the opportunity to acquire, develop and market these drugs. There are also a large number of emerging biotechnology companies doing research in hematology and oncology, many of which do not have the global commercial and regulatory capabilities that we have. We believe we can be a regional or global partner for these companies, particularly for compounds that target smaller patient populations. There are approximately 11,000 hematologists and oncologists practicing in each of the U.S. and Europe. In addition, a small number of opinion leaders significantly influence the types of drugs prescribed by this group of physicians. We believe that we can effectively reach the hematology and oncology markets with a relatively small sales organization focused on these physicians and opinion leaders.

Expanding and leveraging our global sales and marketing capabilities. We believe that our U.S., European and Australian sales and marketing organizations, combined with our distributor network in other countries, distinguish us from other pharmaceutical companies of our size. In each of these markets, we are continuing to develop highly-trained sales forces that target the hematology and oncology communities in

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conjunction with medical education specialists focused on advocate development, educational forums, clinical data publications and clinical development strategies. The licensing of Refludan® and Innohep® were strategically important as they provided the means for us to establish our current sales and marketing organizations. Having these teams in place calling on key hematologists and oncologists will facilitate the commercial launch of our two drugs in registration and makes us a more attractive partner for companies with drugs targeted to this group of physicians. We expect to expand the size of our sales force as we increase sales of Thalidomide Pharmion 50mg in Europe and as needed to support the launch of Vidaza and products licensed in the future from other companies. By managing the global sales and marketing of our products on our own and with our partners, we believe we can provide uniform marketing programs and consistent product positioning and labeling. In addition, we seek consistent pricing across these markets to maximize the commercial potential of our products and reduce the risk of parallel imports and reimportation.

Leveraging our global regulatory expertise. We have assembled a team of highly-experienced regulatory professionals with multinational expertise in obtaining regulatory approvals for new drugs and maintaining compliance with the regulations governing the sales, marketing and distribution of pharmaceutical products. While some early stage biotechnology and pharmaceutical companies have developed regulatory capabilities in the country in which they are located, we have built an organization with multinational regulatory expertise. We believe our regulatory experience enables us to devise time and cost-efficient strategies to obtain regulatory approvals for new drugs, and to choose the regulatory pathway that allows us to get a product to market as quickly as possible. We can use our resources efficiently to generate a regulatory submission that can be used in multiple jurisdictions. Our global regulatory expertise is an essential element of effectively evaluating and developing late-stage product candidates. We believe that this provides us with a competitive advantage in attracting biotechnology and pharmaceutical companies with products in development that they want to out-license.

Acquiring attractive late-stage development or approved products. We intend to continue to acquire or in-license rights to late-stage development and approved products to more fully exploit our regulatory, sales and marketing capabilities. We are focused on acquiring products that satisfy significant unmet medical needs and that provide us with a period of sales, regulatory or geographic exclusivity.

Our Products

Our product portfolio is focused on addressing unmet needs in the hematology and oncology markets. We believe these markets present us with significant commercial opportunities. Our current product portfolio consists of the following:

Product	Disease/Indication	Phase of Development	Licensor	Licensed Territory
Thalidomide Pharmion 50mg (thalidomide)	Relapsed and refractory multiple myeloma	In registration in Europe and approved in Australia and New Zealand; recently initiated compassionate use and named patient sales in Europe	Celgene Corporation and Penn T Limited	All countries outside North America, Japan, China, Taiwan and Korea
	Newly-diagnosed multiple myeloma	Phase III study ongoing		

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Product	Disease/Indication	Phase of Development	Licensor	Licensed Territory
Vidaza (azacitidine)	Myelodysplastic syndromes	In registration in the U.S. with a Subpart H NDA priority review granted. Pre- registration in Europe	Pharmacia & Upjohn Company (Pfizer, Inc.)	Global rights
Innohep® (tinzaparin)	Deep vein thrombosis with or without pulmonary embolisms	Marketed	LEO Pharma A/S	U.S.
Refludan® (lepirudin)	Heparin-induced thrombocytopenia type II	Marketed	Schering AG	All countries outside North America

Thalidomide Pharmion 50mg

In November 2001, we entered into agreements with Celgene Corporation and Penn T Limited to obtain the exclusive marketing and distribution rights to Celgene s formulation of thalidomide, Thalomid®, in all countries outside of North America, Japan, China, Taiwan and Korea. Under the agreement with Celgene, we also obtained an exclusive license in our territory to utilize Celgene s current and future thalidomide-related patents, including its patented System for Thalidomide Education and Prescribing Safety, or S.T.E.P.S.® program, and its current and future thalidomide-related dossiers, including clinical and pharmaceutical formulation data. We recently began selling thalidomide on a compassionate use and named patient basis in Europe while we actively seek full regulatory approval for this drug in Europe and several additional countries. In the fourth quarter of 2003, Thalidomide Pharmion 50mg was approved as a treatment for relapsed and refractory multiple myeloma and ENL in Australia and New Zealand. These approvals were the first regulatory approval of thalidomide for multiple myeloma anywhere in the world. In our markets, we sell Thalomid® as Thalidomide Pharmion 50mg and we call the Celgene S.T.E.P.S.® program the Pharmion Risk Management Program, or PRMP.

Since acquiring these rights from Celgene and Penn, we have undertaken the following activities to commercialize thalidomide in Europe and our additional markets:

Filed marketing authorization applications Beginning in March 2002, we submitted marketing authorization applications to the European Agency for the Evaluation of Medicinal Products, or the EMEA, and the Therapeutic Goods Administration, or the TGA, in Australia and to regulatory authorities in New Zealand, South Africa, Saudi Arabia and Turkey. We are seeking approval for thalidomide as a treatment for relapsed and refractory multiple myeloma and for ENL. In the fourth quarter of 2003, Thalidomide Pharmion 50mg was approved in Australia and New Zealand for these indications.

Acquired Laphal Développement, S.A. In March 2003, we acquired Laphal, the only other company that has submitted a marketing authorization application for thalidomide in Europe. In addition, Laphal was selling its formulation of thalidomide on a compassionate use or named patient basis in France, Belgium and Luxembourg, and we are continuing to sell thalidomide in these markets on a compassionate use or named patient basis.

Assumed Penn s compassionate use and named patient sales in the U.K., Ireland and Denmark Under our initial license agreement with Penn, they were permitted to continue compassionate use and named patient sales of their formulation of thalidomide in the U.K., Ireland and Denmark until we received a marketing authorization from the EMEA. In June 2003, Penn agreed to discontinue its sales of thalidomide in these countries and we initiated sales of Thalidomide Pharmion 50mg on a compassionate use or named patient basis in these countries.

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Initiated compassionate use and named patient sales in Europe In late June 2003, we began compassionate use and named patient sales in the markets previously served by Grünenthal Group, the original manufacturer of thalidomide. Through June 2003, Grünenthal distributed thalidomide free of charge in all European markets, except for those served by Laphal and Penn. In June 2003, Grünenthal announced that it would no longer be providing thalidomide due to the exhaustion of its supply and it referred healthcare professionals seeking thalidomide supply to us.

Developed and implemented the Pharmion Risk Management Program Given thalidomide s history and risk, the development of the PRMP was a critical element to our planned commercialization of thalidomide and enrollment is obligatory for all patients receiving the drug. Shortly after our acquisition of the thalidomide rights from Celgene in 2001, we began to develop the PRMP consistent with Celgene s S.T.E.P.S. This process included the development of software and educational materials in 15 languages for use by physicians, pharmacists and patients throughout Europe and our other markets. We implemented PRMP in June 2003 in connection with the commencement of our compassionate use and named patient sales.

Thalidomide was developed in the late 1950 s as an oral, non-barbiturate sedative and was prescribed throughout Europe for use as a sleep aid and for the treatment of morning sickness in pregnancy. Shortly thereafter, use of thalidomide was found to be associated with severe birth defects and it was virtually withdrawn from the worldwide market, without ever receiving approval in the U.S. In 1964, thalidomide was discovered to be effective in the treatment of ENL, which is an inflammatory complication of leprosy. As a result, thalidomide remained in use as a treatment for ENL. In the 1990s, it was further discovered to act as an anti-angiogenic agent, which is an agent that prevents the formation of new blood vessels. Since many types of tumors are associated with the formation of new blood vessels, physicians began to explore thalidomide s use as a treatment to prevent the growth of tumor-associated blood vessels on the theory that this would result in starvation of the tumor.

In 1998, Celgene s Thalomid® was approved in the U.S. for the treatment of acute cutaneous manifestations of moderate to severe ENL and as maintenance therapy for prevention and suppression of cutaneous manifestation recurrences. Thalomid® was the first drug approved by the FDA under a special restricted distribution for safety regulation. In connection with FDA approval, given the known propensity of thalidomide for causing birth defects, Celgene developed its patented S.T.E.P.S.® program, which is a comprehensive compliance and risk management program designed to support the safe and appropriate use of Thalomid® by ensuring that women of child-bearing potential do not come into contact with Thalomid®. While the treatment of ENL is the only currently approved indication for thalidomide in the U.S., the drug is used primarily in the treatment of multiple myeloma and other forms of cancer, including renal cell carcinoma, which is a cancer of the kidneys, glioblastoma, which is a cancer of the brain, and colon cancer.

Multiple myeloma is the second most common hematological cancer after non-Hodgkin s lymphoma. It is a cancer of the plasma cells in the bone marrow, which is characterized by lytic bone lesions or the production of elevated levels of M-protein, an abnormal monoclonal antibody, in the blood or urine of patients. The symptoms of multiple myeloma include painful bone deterioration, bone marrow failure (anemia, leukopenia and thrombocytopenia), plasma cell leukemia, infections, kidney damage or failure and hyperviscosity of the blood. Although the median age of onset of multiple myeloma is 65 to 70 years of age, according to the Multiple Myeloma Research Foundation, recent statistics indicate both increasing incidence and earlier age of onset. The incidence of multiple myeloma in most western industrialized countries is approximately 4 in every 100,000 persons. We estimate that there are approximately 65,000 multiple myeloma patients in the E.U., with approximately 21,000 new cases annually, and 4,000 to 5,000 multiple myeloma patients in Australia, with approximately 800 new cases annually. While current treatment regimens provide some therapeutic benefit, multiple myeloma patients continue to have high rates of relapse and suffer high mortality rates.

Thalidomide is currently being evaluated as a potential therapy for all stages of multiple myeloma, in particular, newly diagnosed and relapsed and refractory. Several leading investigators at cancer research

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centers have published data on the response rate, the median effective dose and the average duration of response for multiple myeloma patients treated with thalidomide in clinical trials.

Newly Diagnosed Multiple Myeloma. Peer-reviewed studies from MD Anderson Cancer Center and the Mayo Clinic evaluating the use of the orally administered combination of thalidomide and dexamethasone for newly diagnosed multiple myeloma were published in November 2002 in the *Journal of Clinical Oncology.* Dr. S. Vincent Rajkumar of the Mayo Clinic reported that 32 of 50 patients (64 percent) achieved a greater than 50% reduction in M-protein, and an additional 14 patients (28 percent) achieved a reduction in M-protein of between 25 and 50%. These reductions in M-protein are an indication of a positive effect of the drug on the course of this disease. The regimen was generally well-tolerated, and the most commonly reported grade one or two adverse events were constipation, sedation, fatigue, neuropathy, rash, tremor, edema and elevated alkaline phosphatase, a kidney enzyme. Based on this data, Celgene is sponsoring, and we are helping to fund, a Phase III registration study to confirm the benefits of thalidomide plus dexamethasone in newly diagnosed multiple myeloma patients. If successful, we intend to submit this data to the EMEA in support of an indication for Thalidomide Pharmion 50mg as a treatment for newly diagnosed multiple myeloma.

Relapsed and Refractory Multiple Myeloma. Thalidomide s effect on long-term survival in multiple myeloma was published in *Blood* in July 2001 in an article entitled Extended Survival in Advanced and Refractory Multiple Myeloma After Single-agent Thalidomide: Identification of Prognostic Factors in a Phase II Study of 169 Patients. The study is a follow-up of a Phase II trial of 169 advanced and refractory multiple myeloma patients with progressive disease treated with thalidomide, and it extends results of 84 patients previously reported in *The New England Journal of Medicine.* The Phase II study was initiated to evaluate the use of thalidomide in multiple myeloma patients who relapsed after high dose chemotherapy. Of the study s 169 patients, 37% demonstrated a 25% or greater reduction in M-protein, 30% demonstrated a 50% or greater reduction and 14% of patients achieved a complete or near complete response.

The trial s principal investigator, Bart Barlogie, M.D., Ph.D., and researchers at the Arkansas Cancer Research Center reported that high-risk patients who received greater than or equal to 42 grams of thalidomide in a three-month period experienced higher response rates (54% vs. 21%) and longer survival time (63% vs. 45%). In addition, for the entire patientgroup, event-free survival after two years of follow-up was 20%, and two year overall survival was 48%.

The study s most commonly reported side effects included one or more grade three toxicities, which reflect more severe side effects. Approximately 25% of patients experienced events affecting the central nervous system, such as sedation and somnolence, confusion, depression and tremor. Approximately 16% of patients experienced gastrointestinal toxicities, mainly constipation. Neuropathy was seen in 9% of patients, and less than 2% of patients developed deep vein thrombosis. These toxicities were found to be dose related.

In addition to these studies evaluating thalidomide as a therapy for multiple myeloma, there are various Phase II studies ongoing in respect of solid tumors, including renal cell, colorectal cancer, non-small cell lung cancer, prostate cancer, glioblastoma and metastatic melanoma.

Despite the lack of any formal regulatory approval for thalidomide outside the U.S., as a result of compassionate use and named patient sales and the publication of articles reporting on investigator-led clinical trials, thalidomide has become a widely used therapy for the treatment of multiple myeloma and certain other forms of cancer. In Europe, we estimate over 10,000 patients were treated with thalidomide during 2002, with substantially all drug product distributed by three companies. Grünenthal Group, the German company that was the original developer of thalidomide, distributed approximately two-thirds of the overall volume used in Europe free of charge upon physician request through various special regulatory authorizations. In June 2003, Grünenthal announced that due to the exhaustion of its supply, it was discontinuing the distribution of thalidomide. We believe that the remaining thalidomide used in Europe during 2002 was supplied primarily by Penn T Limited and Laphal, the French pharmaceutical development, regulatory and marketing organization that we acquired in March 2003. Both Penn and Laphal supplied thalidomide pursuant to the regulatory

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provisions allowing for sale of unlicensed drugs on a compassionate use or named patient basis. While the thalidomide supplied by Penn and Laphal was not given free of charge, it was sold at a significant discount to the price charged by Celgene in the U.S.

In March 2002, working with the data packages that we had obtained from Celgene and Penn, we submitted to the EMEA, under its centralized procedure, two marketing authorization applications for thalidomide for the treatment of relapsed and refractory multiple myeloma and for ENL. In February 2003, we withdrew our marketing authorization application for ENL to focus our efforts with the EMEA on obtaining the marketing authorization for relapsed and refractory multiple myeloma. This decision was made in consultation with the EMEA, which, given their belief that thalidomide would have widespread off-label use in the treatment of multiple myeloma, was not comfortable approving thalidomide for the much narrower indication of ENL, especially given the history of thalidomide in Europe.

In addition to these EMEA regulatory approval activities, we have submitted regulatory approval applications for thalidomide in Australia, South Africa, Saudi Arabia and Turkey for the indications of multiple myeloma and ENL. In the fourth quarter of 2003, the TGA approved the use of Thalidomide Pharmion 50mg for treatment of relapsed and refractory multiple myeloma and ENL in Australia. This was the first approval of Thalidomide for the treatment of multiple myeloma, after failure of standard therapies, anywhere in the world.

We were granted orphan drug designation for thalidomide in Europe by the EMEA for the multiple myeloma indication, which, if the marketing authorization application is approved and the criteria for orphan drug designation continue to be met, would provide a ten year period of exclusivity from the date of the marketing authorization application s approval. During this period the EMEA would be prohibited, except in very limited circumstances, from approving another formulation of thalidomide for treatment of relapsed and refractory multiple myeloma. We were also granted orphan drug designation for thalidomide in Australia, as well as data exclusivity, which provides similar protection for a five year period from the date of approval.

In March 2003, through our purchase of all of the outstanding stock of Gophar S.A.S., we acquired Laphal, which sells its formulation of thalidomide, known as Thalidomide Laphal, in France and Belgium under an *autorisation temporaire d utilisation,* or ATU, which is a temporary authorization for compassionate use sales.

For its fiscal year ended December 31, 2002, Laphal had aggregate net sales of $5.5 million, substantially all of which were sales of Thalidomide Laphal. Our acquisition of Laphal, also allowed us to obtain its two marketing authorization applications on file with the EMEA for thalidomide. These two marketing authorization applications are for thalidomide as a treatment for ENL and for relapsed and refractory multiple myeloma, both of which have been granted orphan drug status by the EMEA. Laphal had also undertaken a number of clinical trials of thalidomide, the data from which may be useful to us in connection with our efforts to seek marketing approval from the EMEA. We are currently responding to questions posed by the EMEA to each of our active marketing authorization applications on file. We anticipate submitting our responses for the two multiple myeloma applications during the second quarter of 2004. With our acquisition of Laphal, to our knowledge we are now the only company with applications with the EMEA for a thalidomide marketing authorization.

We believe that an integral component of our applications is our undertaking to develop and implement the PRMP throughout Europe and our other markets. The PRMP requires adherence to strict guidelines both prior to and during the course of thalidomide therapy, including comprehensive physician, pharmacist and patient registration and education, emphasizing, among other things, the need for adequate contraception in patients taking thalidomide and pregnancy tests for female patients of child-bearing potential. Under the PRMP, automatic prescription refills are prohibited, and prescriptions may not exceed four weeks dosing. The PRMP also permits authorization of each prescription only upon confirmation of compliance with the PRMP guidelines.

We became aware of Grünenthal s intention to discontinue distributing thalidomide in the fourth quarter of 2002 and recognized that this would create a large void in the supply of thalidomide for the thousands of

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patients currently being treated with the drug in Europe, Australia and many Asian countries. We also believed that patients and medical professionals would benefit from a more tightly controlled distribution system for thalidomide, such as the PRMP. As such, in the fourth quarter of 2002, we began to actively work with the regulatory authorities in each of the major European countries to fully explain to them the benefits of the PRMP and to obtain authorizations, where required, to allow us to sell thalidomide on a compassionate use or named-patient basis prior to the issuance of a formal marketing authorization. Following negotiations with the health authorities of individual countries, while we pursue a marketing authorization, we began selling Thalidomide Pharmion 50mg in June 2003 on a compassionate use and named patient basis in Europe, South Africa and Egypt and we have made the PRMP program available in over 20 languages. Since receiving regulatory approval to market Thalidomide Pharmion 50 mg in Australia and New Zealand during the fourth quarter of 2003, we have been actively marketing the product in each of those countries. In addition, we are continuing to sell Thalidomide Laphal in France and Belgium until such time as we are permitted to replace this formulation with Thalidomide Pharmion 50mg.

Under our original agreement with Penn, they were permitted to continue compassionate use and named patient sales of their formulation of thalidomide in the U.K., Ireland and Denmark. In June 2003, Penn agreed to discontinue its sales of thalidomide in these countries and we initiated sales of Thalidomide Pharmion 50mg on a compassionate use or named patient basis in these countries. This revised arrangement reflected Penn s recognition of the merits of using the PRMP in connection with thalidomide sales in these countries.

Vidaza

In June 2001, we entered into an agreement with Pharmacia & Upjohn Company, now part of Pfizer, Inc., to obtain the exclusive worldwide manufacturing, marketing and distribution rights to azacitidine, which we intend to market as Vidaza. Under the agreement with Pharmacia, we also obtained an exclusive worldwide license to use Pharmacia s azacitidine technology and patents, including its clinical data. Azacitidine was the subject of a completed and published Phase III study demonstrating its safety and efficacy in the treatment of myelodysplastic syndromes, or MDS, a group of hematologic conditions caused by abnormal blood-forming cells of the bone marrow.

Azacitidine, a pyrimidine nucleoside analog, was originally developed by Upjohn Corporation as a cytotoxic agent, which is an agent that indiscriminately kills actively multiplying cells. Azacitidine was studied at high doses as a treatment for various malignancies, including acute myelogenous leukemia, or AML. An NDA was submitted by Upjohn in 1982 for the treatment of AML, but was deemed not approvable by the FDA, due to a lack of controlled studies adequately demonstrating clinical benefit. In addition, there were severe side effects observed in the high dosage studies. Researchers at the NCI, The Mount Sinai Medical Center and other institutions continued to study azacitidine and determined that it could be used effectively at much lower doses than originally studied by Upjohn, thereby reducing the side effects experienced in the earlier clinical studies. The results of subsequent clinical studies suggest that azacitidine is an effective treatment for MDS.

The recognition that azacitidine could be effective at lower doses was based on the discovery that azacitidine acts not only as a cytotoxic agent, but also through an additional mechanism of action. Azacitidine is a member of a class of drugs in development known as hypomethylating or demethylating agents. Methylation of DNA is a major mechanism regulating gene expression. Researchers have determined that an increase in specific methylation of DNA results in blockage of the activity of genes that regulate cell division and differentiation, known as suppressor genes. With suppressor genes blocked, cell division becomes unregulated, causing cancer. In studies, researchers have demonstrated that azacitidine can reverse the methylation of DNA, leading to reexpression of suppressor genes and a resulting redifferentiation and maturation of the cancer cells back to normal.

MDS occurs when blood cells remain in an immature, or blast, stage within the bone marrow and never develop into mature cells capable of performing their necessary functions. The five types of MDS are refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia. Approximately 90% of

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MDS cases occur in persons aged 60-80. According to the American Cancer Society, or ACS, the exact number of cases of MDS in the U.S. is unknown, as there is no registry tracking this information, but most estimates are between 10,000 and 20,000 new cases each year. According to the ACS, these numbers appear to be increasing each year. Currently, we estimate there are approximately 50,000 to 60,000 MDS patients throughout the U.S. and Europe. According to the ACS, survival rates range from six months to six years for the different types of MDS. MDS can result in death from bleeding and infection in the majority of patients, while transformation to AML occurs in up to 40% of patients. Following transformation to AML, these patients have an exceptionally poor prognosis. MDS may occur without any identifiable cause, may be related to chemotherapy or radiation therapy being administered to treat other diseases, or may result from exposure to petrochemicals, benzene or rubber. Despite having been the subject of significant clinical development activity, there is currently no approved treatment for MDS. Patients generally receive best supportive care, which typically consists of a combination of transfusions, antibiotics and growth factors, such as erythropoietin and granulocyte colony stimulating factor. In addition, clinicians may add low-dose chemotherapies to best supportive care if they feel that their patients can tolerate the side effects. Patients under 60 years of age may receive bone marrow transplants.

In a Phase III study, azacitidine demonstrated superior efficacy compared to best supportive care, including improved response rates and delayed time to leukemic transformation or death. Azacitidine s effect on MDS was published in the Journal of Clinical Oncology in an article entitled Randomized Controlled Trial of azacitidine in Patients With the Myelodysplastic Syndrome: A Study of the Cancer and Leukemia Group B. Dr. Lewis R. Silverman of the Mount Sinai Medical Center and his colleagues reported that they conducted a randomized controlled trial in 191 patients comparing the effects of azacitidine and best supportive care on various hematological parameters. Azacitidine was given by subcutaneous injection. Responses occurred in 60% of patients in the azacitidine group (7% complete response, 16% partial response, 37% improved) compared with 5% (improved) of the patients receiving best supportive care, a statistically significant response. Median time to leukemic transformation or death was 21 months for azacitidine and 13 months for best supportive care, also a statistically significant response. The most common toxicity of azacitidine was myelosuppression, a reduction in the ability of the bone marrow to produce blood cells, and nausea.

In addition to the efficacy data from the Silverman study, several quality of life parameters were also reported and showed statistically significant improvement in the azacitidine patient group compared to patients receiving best supportive care. In particular, azacitidine patients showed statistically significant improvement over time in fatigue, physical functioning and shortness of breath. In patients receiving best supportive care who showed stable or worsening quality of life prior to crossover to azacitidine, statistically significant improvement occurred in fatigue, physical functioning, shortness of breath and general well-being after crossover to azacitidine.

In December 2003, we submitted an NDA for Vidaza, under Subpart H of the New Drug Application regulations, which allows for conditional approval of a drug to treat serious or life-threatening diseases based on a surrogate endpoint, a relatively simple measure of the effect of a drug on the course of a disease, as long as the drug provides a meaningful therapeutic benefit over existing treatments. In addition, under Subpart H a drug can be approved on the basis of one Phase I or Phase II study, conditioned upon the sponsor agreeing to complete a confirmatory Phase IV study. Since there are currently no drugs approved for the treatment of MDS and best supportive care is the only existing treatment, the Subpart H approval option is available. In February 2004, the FDA accepted for filing and granted Priority Review classification for our Vidaza NDA. Priority Review status of the NDA reduces the standard FDA response time to six months, and targets an agency response on or before June 29, 2004.

Our submission is based upon the previously cited Silverman study for the treatment of MDS that was conducted by the Cancer and Leukemia Group B, or CALGB, and the NCI and two supportive Phase II CALGB/ NCI studies. Due to the fact that the Phase III CALGB study was not prospectively designed as a registration study, over the last 24 months we have engaged in a lengthy process of collecting and analyzing data from the CALGB studies to confirm their published results and to compile the information needed to submit an NDA for Vidaza in MDS. This activity involved visiting nearly 75 treatment centers and accessing

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and auditing nearly 400 patient records from the CALGB studies. In addition, working with third party manufacturers, we have successfully developed a fully scaled up manufacturing process for the active ingredient and finished product.

As required under Subpart H in the U.S., we have initiated a comparative confirmatory clinical trial that will examine survival outcomes and other secondary end points, using a multicenter, randomized, open-label, parallel group format. The aim of this study is to compare the effect of Vidaza plus best supportive care against conventional care regimens plus best supportive care on survival in MDS patients. As a result of the fact that this study is global in nature and MDS treatment practices vary among countries, there will be three comparative conventional care treatments: best supportive care only; low dose cytarabine, plus best supportive care; or standard chemotherapy, plus best supportive care. This design takes into account the actual conventional care used to treat MDS patients in each country targeted for trial participation and should also help to enhance timely enrollment. The study will recruit over 350 patients and will be one of the largest studies to date in this disease.

The primary objective of this confirmatory study is to look at survival in these MDS patients. All other relevant endpoints, such as time to transformation to AML, time to relapse after complete remission or partial remission, disease progression, hematological status (peripheral blood counts, need for platelet and red blood cell transfusions and hematological response), episodes of infections requiring intravenous antibiotics and safety parameters will be assessed.

Innohep®

Innohep®, the tradename for tinzaparin, is a low molecular weight heparin that is approved in the U.S. and 63 other markets. In July 2002, we entered into an agreement with LEO Pharma A/S to obtain the exclusive U.S. marketing and distribution rights to Innohep®. Since LEO Pharma does not have a presence in the U.S., it sought to market the product in the U.S. through a marketing partner. It originally chose DuPont Pharmaceuticals Company, which launched Innohep® in the U.S. in late 2000 following its approval by the FDA in June of that year. Shortly after Innohep® s launch, DuPont s pharmaceutical business was acquired by Bristol Myers Squibb, which elected to return the U.S. rights to the product back to LEO Pharma. As a result, while the product has achieved substantial sales in Europe and elsewhere around the world, Innohep® received minimal marketing support in the U.S. throughout 2001 and 2002.

Innohep® is a member of a broad class of drugs known as anticoagulants, which are generally prescribed to prevent or treat blood clotting in patients. In the U.S., Innohep® is approved for the treatment of acute, symptomatic deep vein thrombosis, or DVT, which is a subset of the overall anticoagulant market. DVT occurs when a blood clot develops in the deep veins of the legs. If not effectively treated, DVT can lead to pulmonary embolisms that, in turn, can result in death. Cancer patients are particularly at risk to develop DVT, either from the disease itself or as a side effect of certain cancer treatments. The estimated prevalence of DVT in cancer patients ranges from 15-20%. Further, according to the ACS, approximately 1.3 million new cases of cancer occur in the U.S. each year. We believe that 21%, or approximately 277,000, of these patients are highly predisposed to DVT occurrence.

The acquisition of the marketing and distribution rights to Innohep® allowed us to establish our sales and marketing organization in the U.S. in a cost-effective manner, and provided us with access and exposure to the opinion leaders that influence product sales in the hematology and oncology markets. We completed the hiring and training of our U.S. sales force and relaunched Innohep® in October 2002. Innohep® is administered through a subcutaneous injection once daily for at least a six day cycle.

We attribute the growth we have experienced in Innohep® sales to our strategy of focusing our marketing efforts on hematologists and oncologists, groups often overlooked by pharmaceutical companies marketing other anticoagulants. Hematologists and oncologists are among the top three prescribers of DVT treatments. We believe, however, that only a small number of the sales calls made to DVT treatment prescribers are made to hematologists and oncologists. Innohep® does not require a dosing adjustment for weight-compromised, elderly or renally-impaired patients. Because these are common conditions for cancer patients, we believe that

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this feature, combined with the convenience of its once per day dosing, makes Innohep®the treatment of choice for a cancer patient with DVT.

Innohep® is used predominantly as a treatment for DVT since this is its only approved indication. In order to achieve the long-term sales potential that we believe Innohep® has, use of the drug will need to be expanded into other areas. One area of particular interest is the use of Innohep® for the prevention of DVT in high-risk cancer patients. Our development strategy for Innohep® includes funding clinical studies, that examine the use of Innohep® in prevention and treatment of DVT in cancer patients to generate data suitable for publication.

Refludan®

Refludan®, the tradename for lepirudin, is an antithrombin agent for patients with heparin-induced thrombocytopenia type II, or HIT type II. Refludan® is approved in 42 countries outside of North America. In May 2002, we entered into an agreement with Schering AG to obtain the exclusive marketing and distribution rights to Refludan® in all markets outside of North America. Hoechst Marion Roussel, or HMR, originally developed Refludan®. As a condition to the merger of HMR with Rhone Poulenc Rorer to form Aventis Pharmaceuticals, Aventis divested itself of Refludan® on a global basis to Schering AG, which continues to market the product in the U.S. and Canada through its subsidiary, Berlex Laboratories, Inc. Although approved in 42 countries outside of North America, Aventis had actively marketed the product only in Germany. We are currently marketing Refludan® principally in Europe and Australia.

HIT is an allergic, adverse immune response to heparin. Generally this response occurs after 2 to 4 days of heparin exposure, resulting in an absence of sufficient cell platelets to enable blood clotting. HIT occurs in 2-3% of patients treated with unfractionated heparin and 1-2% of patients treated with low molecular weight heparins. There are two forms of HIT. The first is relatively benign. The second, known as HIT type II, is a more serious form with the potential for significant impact on patient morbidity and mortality. Refludan® is prescribed for the treatment of HIT type II. Refludan® is administered through subcutaneous injection or infusion.

We believe that increasing the awareness of HIT and the clinical importance of effectively treating this condition will positively impact its diagnosis and treatment. Beginning in October 2002 and continuing through February 2004, we organized a number of symposia among leading hematologists in Europe, which we called HIT Schools, to provide these specialists with the latest information about HIT and its impact, as well as appropriate treatment regimens. These medical education programs have been our primary marketing activity as we work to build awareness of HIT. Nevertheless, given the relatively low incidence rate for HIT, we do not expect Refludan® sales to grow significantly above the current level. In addition, we expect the potential for Refludan® sales growth to be limited as a result of the warning letter Schering issued to doctors in Germany, following the advice of the EMEA, regarding the incidence of anaphylaxis, a severe allergic reaction, in approximately a dozen patients treated with Refludan® in both the U.S. and Europe, five of which cases resulted in fatalities. Although the possibility of anaphylaxis from Refludan® is a known possible reaction and is indicated in the product s label, the occurrences referenced in the warning letter appeared to be at a higher frequency than had previously been reported.

In addition to adding a marketed product to our portfolio, the acquisition of Refludan® allowed us to achieve our objective of establishing a sales and marketing organization throughout Europe and our other non-U.S. markets. The primary target physician audience for Refludan® is hematologists. With the planned launch of thalidomide and, later, Vidaza, it was important that we develop our commercial organization and establish relationships with the key prescribers of these products. We were able to achieve that objective in Europe through our acquisition of Refludan®. Today we have sales and marketing organizations established in each of the primary European markets, Australia, and, through third party distributors, in 20 additional countries throughout Europe and Asia.

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Sales, Marketing and Distribution

We have established sales and marketing organizations in the U.S., Europe and Australia. Our U.S. field-based sales organization consists of 31 professionals, including 22 clinical account specialists, three sales managers, three medical science liaisons, and three national account specialists. Our clinical account specialists and sales managers average over 10 years pharmaceutical sales experience and are based in or around major metropolitan areas with large inpatient and outpatient cancer treatment centers. Currently, they target hematologists and oncologists who prescribe high volumes of cancer therapies as well as low molecular weight heparin products. The concentration of high volume prescribers enables us to promote Innohep® with a small, dedicated sales and marketing organization. In anticipation of a Vidaza approval in the U.S., we expect to increase the number of field-based professionals to approximately sixty. While the number of target physicians would expand, we believe we can still access key opinion leaders and prescribers with a relatively small sales force.

In Europe, we employ a general manager in each of the U.K., France, Germany, Spain, Italy, and Denmark. These general managers are responsible for all commercial activities in each of their home countries, and may also have responsibility for commercial activities in smaller nearby countries. Each of our subsidiaries employs, in addition to the general manager, a trained physician, regulatory specialists if required by local law, sales representatives, PRMP experts and administrative support staff. In general, we only employ nationals in each of our local subsidiaries. All marketing activities are centrally directed from our U.K. office to ensure consistency across regional markets. In addition, clinical development, regulatory affairs and information technology functions are centrally managed from our U.K. office. In this manner, we seek to develop globally consistent programs but ensure that they are implemented according to local practices. Our Australian sales and marketing organizational structure is consistent with our European structure. Information regarding geographic areas is included in Note 3 to the Consolidated Financial Statements.

In addition to our own sales organizations, we have access to the hematology and oncology markets in 20 additional countries through relationships with our distributors. Pursuant to the agreements governing our relationships with our distributors, we are prohibited from selling or marketing our products on our own behalf in a country covered by one of these agreements until the applicable agreement expires.

The chart below identifies the countries which are served directly by our sales organizations and those which we access using our third-party distribution network.

Direct Sales Countries

Australia	Germany	Spain
Belgium	Ireland	Sweden
Denmark	Italy	Switzerland
Finland	Netherlands	U.K.
France	Norway	U.S.
	Portugal	

Distribution Countries

Cyprus	Lebanon	South Africa
Egypt	Malaysia	Syria
Greece	Malta	Taiwan
Hong Kong	New Zealand	Thailand
Israel	Oman	Turkey
Jordan	Saudi Arabia	United Arab Emirates
Kuwait	Singapore	

By working closely with top scientists, physicians and association leaders, our sales and marketing professionals are able to create science-based marketing materials of interest to key opinion leaders. In addition, our product acquisition strategy has been designed to maximize the success of our sales and marketing efforts by focusing on the acquisition of products and product candidates that make a clinical

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difference to patients in markets responsive to key opinion leaders. We intend to seek new countries in which to promote our products and we will continue the expansion of our sales and marketing organization as product growth or product acquisitions warrant.

In the U.S., we sell to pharmaceutical wholesalers, who in turn distribute product to retail pharmacies, hospitals, and other institutional customers. In Europe and Australia, we sell directly to retail and hospital pharmacies. Sales into countries where we have partnered with third party distributors are made directly to our partners. Net sales generated from three wholesale customers in the U.S. totaled approximately 13% of our total net sales for the year ended December 31, 2003.

Regulatory and Medical Affairs

Our regulatory affairs group is comprised of professionals with experience from both large pharmaceutical companies and biotechnology companies. The difference between an attractive drug candidate and one which is not economically viable for development often hinges on our assessment of the time and expense required to get the drug approved and sold in a particular jurisdiction. Determining the optimal regulatory pathway for commercialization is an integral part of our product candidate selection. We believe that our combination of country-specific regulatory expertise and our focus on the hematology and oncology markets provide a significant advantage as we seek to acquire additional product candidates through in-license, and move our existing product candidates forward through the approval process.

Collaborations and License Agreements

Celgene and Penn Agreements. In 2001, we licensed rights relating to thalidomide from both Celgene and Penn T Limited for all countries outside of North America, Japan, China, Korea and Taiwan. Under agreements with Celgene, we obtained the rights in this territory to Celgene s formulation of thalidomide, Thalomid®, exclusive licenses or sublicenses for use in this territory of all intellectual property owned or licensed by Celgene relating to thalidomide, as well as all existing and future clinical data relating to thalidomide developed by Celgene, and an exclusive license to employ Celgene s patented S.T.E.P.S.® program as our PRMP. Under agreements with Penn, we became Penn s exclusive distributor in this territory of any formulation of thalidomide manufactured by Penn, which included an exclusive supply and requirements relationship with respect to Penn s manufacture of thalidomide for this territory. We will pay Penn and Celgene a combined royalty of 36% of net sales, less our purchase price from Penn of the units of product sold, on all of our sales of thalidomide once thalidomide is approved by the appropriate health regulatory authority for sale in any country within our license territory. In the interim, our combined royalty payment obligations to Celgene and Penn are generally lower than 36%. Our royalty payment obligations to Celgene and Penn are also subject to certain minimum yearly payment thresholds. In connection with our ongoing relationship with Celgene, and to further the clinical development of thalidomide, particularly in multiple myeloma, we have also agreed to fund an aggregate of $8.0 million of Celgene s clinical trial development costs for clinical studies of thalidomide, with this amount payable in installments through 2005. Through December 31, 2003, we had funded $3 million of this $8 million commitment. The agreements with Celgene and Penn each have a ten year term running from the date of receipt of our first regulatory approval for thalidomide in the United Kingdom, subject, in the case of the Celgene agreement to Celgene having a right to terminate the agreement if we have not obtained that approval by November 2006.

Pharmacia Agreement

We licensed worldwide rights to azacitidine from Pharmacia & Upjohn Company, now a part of Pfizer, Inc., in June 2001. Under the terms of our agreement, we are obligated to pay Pharmacia a royalty of 20% on net sales of Vidaza, except if the data from the clinical trials of the NCI and CALGB on the use of Vidaza as a treatment for MDS patients is deemed insufficient by the FDA to support an approval of Vidaza and we are required to conduct another Phase III clinical trial for MDS prior to initial FDA approval, then the royalty rate will be 8%. The license from Pharmacia has a term extending for the longer of the last to expire of valid patent claims in any given country or ten years from our first commercial sale of the product in a particular country.

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LEO Pharma Agreement

In July 2002, we obtained an exclusive license from LEO Pharma A/S to distribute Innohep® in the U.S., as well as an exclusive supply and requirements agreement with LEO Pharma for their supply to us of Innohep®. Under our agreement with LEO Pharma, we made an up-front payment for this license of $7.5 million, up to $2.5 million of which is creditable against royalty payments otherwise due during the period ending March 1, 2005. In addition, we are obligated to pay LEO Pharma royalties at the rate of 30% on annual net sales of up to $20.0 million and at the rate of 35% of annual net sales exceeding $20.0 million, less in each case our purchase price from LEO Pharma of the units of product we sell. The agreement has a term of ten years.

Schering AG Agreement

In May 2002, we obtained the exclusive rights from Schering AG to distribute Refludan® in all countries outside of North America. Schering produces the product for us under contract with a third-party manufacturer and sells it to us at its acquisition cost plus 5%. Our agreements with Schering, as amended, transfer to us all of the marketing authorizations and product registrations for Refludan® in the individual countries within our territory. We have paid Schering an aggregate of $5.0 million and are obligated to make an aggregate of $8 .0 million of additional fixed payments to Schering, payable in quarterly installments of $1.0 million through the end of 2005. We are obligated to make up to $7.5 million of additional payments upon the achievement of certain milestones. We paid to Schering, in addition to our product acquisition costs, a royalty of 8% of our net sales of Refludan® during the period through December 31, 2003 and pay a royalty of 14% of our net sales of Refludan® thereafter. However, when we have paid $12.0 million in royalties measured from January 2004, the royalty rate would then be reduced to 6%.

CALGB Agreement

In November 2001, we entered into a collaboration agreement with the CALGB pursuant to which the CALGB agreed to provide us with the data produced by its azacitidine studies in exchange for aggregate payments of approximately $1.1 million. We incorporated the data provided to us by the CALGB in our December 2003 NDA submission. The CALGB has agreed not to permit any other party to use its azacitidine data in connection with an NDA until such time as we cease our efforts to commercialize azacitidine.

Manufacturing

We currently use, and expect to continue to be dependent upon, contract manufacturers to manufacture each of our products. We do not maintain alternative manufacturing sources for any of our products. Our contract manufacturers and distributors are subject to extensive governmental regulation. Regulatory authorities in our markets require that drugs be manufactured, packaged and labeled in conformity with Good Manufacturing Practices, or cGMPs. We have established a quality control and quality assurance program, including a set of standard operating procedures and specifications, designed to ensure that our products are manufactured in accordance with cGMPs, and other applicable domestic and foreign regulations.

Thalidomide. We obtain our two formulations of thalidomide from two different suppliers. Thalidomide Pharmion 50mg is formulated, encapsulated and packaged for us by Penn Pharmaceuticals Services Limited of Great Britain in a facility that is in compliance with the regulatory standards of each of the countries where we sell and expect to sell the product. Under the terms of this agreement we purchase from Penn all of our requirements of the product. Pricing is subject to an annual adjustment based upon the fully allocated cost of manufacture. This agreement terminates upon the tenth anniversary of the date upon which we receive regulatory approval for thalidomide in the U.K.

Thalidomide Laphal is formulated, encapsulated and packaged for us by Laphal Industrie, an unaffiliated Company, in a facility that is in compliance with the regulatory standards of each of the countries where we sell and expect to sell the product. Pricing is subject to an annual adjustment based upon a formula that accounts for increases in the cost of manufacture. In addition, in the event that prior to the expiration of the agreement we decide to discontinue ordering Thalidomide Laphal from Laphal Industrie, we are obligated to

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provide twelve months advance notice and pay 300,000. If our notice to discontinue ordering Thalidomide Laphal is not timely, the fee may increase to as much as 500,000. This agreement terminates in March 2013.

Vidaza. Under the terms of two development agreements, Ash Stevens, Inc. and Ben Venue Labs provide us with clinical supplies and manufacturing services for azacitidine. Azacitidine drug substance is manufactured for us by Ash Stevens, who sends the product in its raw form to Ben Venue Labs. Ben Venue Labs then formulates the product, fills the product into vials and labels the finished product for us. Both Ash Stevens and Ben Venue Labs operate facilities that are in compliance with the regulatory standards of each of the countries where we expect to sell the product. We expect to enter into commercial supply agreements with both Ash Stevens and Ben Venue prior to receiving regulatory market approval for azacitidine.

Innohep®. Innohep® is formulated and packaged for us by LEO Pharmaceutical Products Ltd. in a facility that is in compliance with FDA requirements. Under our agreement, we are required to purchase our Innohep® requirements exclusively from LEO. Pricing may be adjusted annually based upon changes in the Danish Pay Index. This agreement terminates in June 2012.

Refludan®. Refludan® is manufactured in a facility that meets the standards of each of the countries where we sell and expect to sell the product by a third-party manufacturer, who then supplies the drug to our supplier, Schering AG. Under our agreement, we are required to purchase our Refludan® requirements exclusively from Schering. The pricing is subject to an annual adjustment under the existing supply agreement between Schering and the third-party manufacturer. This agreement terminates in 2022.

Raw Materials

Raw materials and supplies are normally available in quantities adequate to meet the needs of our business.

Government Regulation

Regulation by governmental authorities in the U.S. and other countries is a significant factor in the manufacture and marketing of our products and in ongoing research and product development activities. All of our products require regulatory approval by governmental agencies prior to commercialization. In particular, our products are subject to rigorous preclinical and clinical testing and other approval requirements by the FDA and similar regulatory authorities in other countries. Various statutes and regulations also govern or influence the manufacturing, safety, reporting, labeling, storage, record keeping and marketing of our products. The lengthy process of seeking these approvals, and the subsequent compliance with applicable statutes and regulations, require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could harm our business.

The regulatory requirements relating to the manufacturing, testing and marketing of our products may change from time to time. For example, at present, member states in the E.U. are in the process of incorporating into their domestic laws the provisions contained in the E.U. Directive on the implementation of good clinical practice in the conduct of clinical trials. The Directive imposes more onerous requirements in relation to certain aspects of clinical trial conduct than are currently in place in many member states. This may impact our ability to conduct clinical trials and the ability of independent investigators to conduct their own research with support from us. In addition, the E.U. rules concerning the authorization of medicinal products are in the process of being amended. We do not expect the new rules to apply until 2005. The final rules are not yet available and as such the impact upon our business cannot be known at this time.

Product Approval

The clinical development, manufacturing and marketing of our products are subject to regulation by various authorities in the U.S., the E.U. and other countries, including, in the U.S., the FDA, and, in the E.U., the EMEA. The Federal Food, Drug, and Cosmetic Act, the Public Health Service Act in the U.S. and numerous directives, regulations, local laws and guidelines in the E.U. govern the testing, manufacture, safety, efficacy, labeling, storage, record keeping, approval, advertising and promotion of our products. Product

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development and approval within these regulatory frameworks takes a number of years and involves the expenditure of substantial resources.

Regulatory approval will be required in all the major markets in which we, or our licensors, seek to test our products in development. At a minimum, such approval requires the evaluation of data relating to the quality, safety and efficacy of a product for its proposed use. The specific types of data required and the regulations relating to this data will differ depending on the territory, the drug involved, the proposed indication and the stage of development.

In general, new chemical entities are tested in animals until adequate proof of safety is established. Clinical trials for new products are typically conducted in three sequential phases that may overlap. In Phase I, the initial introduction of the pharmaceutical into healthy human volunteers, the emphasis is on testing for safety (adverse effects), dosage tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase II involves studies in a limited patient population to determine the initial efficacy of the pharmaceutical for specific targeted indications, to determine dosage tolerance and optimal dosage and to identify possible adverse side effects and safety risks. Once a compound shows evidence of effectiveness and is found to have an acceptable safety profile in Phase II evaluations, Phase III trials are undertaken to more fully evaluate clinical outcomes.

In the U.S., specific preclinical data and chemical data, as described above, needs to be submitted to the FDA as part of an Investigational New Drug application, or IND, which, unless the FDA objects, will become effective 30 days following receipt by the FDA. Phase I studies in human volunteers may commence only after the application becomes effective. Prior regulatory approval for human healthy volunteer studies is also required in member states of the E.U. Currently, in each member state of the E.U., following successful completion of Phase I studies, data is submitted in summarized format to the applicable regulatory authority in the member state in respect of applications for the conduct of later Phase II studies. The regulatory authorities in the E.U. typically have between one and three months in which to raise any objections to the proposed study, and they often have the right to extend this review period at their discretion. In the U.S., following completion of Phase I studies, further submissions to regulatory authorities are necessary in relation to Phase II and III studies to update the existing IND. Authorities may require additional data before allowing the studies to commence and could demand that the studies be discontinued at any time if there are significant safety issues. In addition to the regulatory review, a study involving human subjects has to be approved by an independent body. The exact composition and responsibilities of this body will differ from country to country. In the U.S., for example, each study will be conducted under the auspices of an independent Institutional Review Board at the institution at which the study is conducted. This board considers among other things, the design of the study, ethical factors, the safety of the human subjects and the possible liability risk for the institution. Equivalent rules apply in each member state of the E.U. where one or more independent ethics committees, which typically operate similarly to an Institutional Review Board, will review the ethics of conducting the proposed research. Other authorities around the rest of the world have slightly differing requirements involving both the execution of clinical trials and the import/export of pharmaceutical products. It is our responsibility to ensure we conduct our business in accordance with the regulations of each relevant territory.

Information generated in this process is susceptible to varying interpretations that could delay, limit or prevent regulatory approval at any stage of the approval process. The failure to demonstrate adequately the quality, safety and efficacy of a therapeutic drug under development would delay or prevent regulatory approval of the product. There can be no assurance that if clinical trials are completed, either we or our collaborative partners will submit applications for required authorizations to manufacture and/or market potential products (including a marketing authorization application, NDA or abbreviated NDA) or that any such application will be reviewed and approved by the appropriate regulatory authorities in a timely manner, if at all.

In order to gain marketing approval we must submit a dossier to the relevant authority for review, which is known in the U.S. as an NDA and in the E.U. as a marketing authorization application, or MAA. The format is usually specific and laid out by each authority, although in general it will include information on the

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quality of the chemistry, manufacturing and pharmaceutical aspects of the product as well as the non-clinical and clinical data. The FDA undertakes the review for the U.S. In the E.U. there is, for many products, a choice of two different authorization routes: centralized and decentralized. Under the centralized route one marketing authorization is granted for the entire E.U., while under the decentralized route a series of national marketing authorizations are granted. In the centralized system the application will be reviewed by members of the Committee for Proprietary Medicinal Products, or the CPMP, on behalf of the EMEA. The EMEA will, based upon the review of the CPMP, provide an opinion to the European Commission on the safety, quality and efficacy of the product. The decision to grant or refuse an authorization is made by the European Commission. In circumstances where use of the centralized route is not mandatory, we can choose to use the decentralized route, in which case the application will be reviewed by one member state s regulatory agency. If the regulatory agency grants the authorization, other member states regulatory authorities are asked to mutually recognize the authorization granted by the first member state s regulatory agency. Approval can take several months to several years, or be denied. The approval process can be affected by a number of factors. Additional studies or clinical trials may be requested during the review and may delay marketing approval and involve unbudgeted costs. The regulatory authorities may conduct an inspection of relevant facilities, and review manufacturing procedures, operating systems and personnel qualifications. In addition to obtaining approval for each product, in many cases each drug manufacturing facility must be approved. Further inspections may occur over the life of the product. An inspection of the clinical investigation sites by a competent authority may be required as part of the regulatory approval procedure. As a condition of marketing approval, the regulatory agency may require post-marketing surveillance to monitor for adverse effects, or other additional studies as deemed appropriate. After approval for the initial indication, further clinical studies are usually necessary to gain approval for any additional indications. The terms of any approval, including labelling content, may be more restrictive than expected and could affect the marketability of a product.

The FDA offers an accelerated approval procedure for certain drugs under Subpart H of the agency s NDA approval regulations. Subpart H provides for accelerated NDA approval for new drugs intended to treat serious or life-threatening diseases where the drugs provide a meaningful therapeutic advantage over existing treatment. Under this accelerated approval procedure, the FDA may approve a drug based on evidence from adequate and well-controlled studies of the drug s effect on a surrogate endpoint that reasonably suggest clinical benefits, or on evidence of the drug s effect on a clinical endpoint other than survival or irreversible morbidity. This approval is conditioned on the favorable completion of trials to establish and define the degree of clinical benefits to the patient. These post-approval clinical trials, known as Phase IV trials, would usually be underway when the product obtains this accelerated approval. If, after approval, a Phase IV trial establishes that the drug does not perform as expected, or if post-approval restrictions are not adhered to or are not adequate to ensure the safe use of the drug, or other evidence demonstrates that the product is not safe or effective under its conditions of use, the FDA may withdraw approval. This accelerated approval procedure for expediting the clinical evaluation and approval of certain drugs may shorten the drug development process by as much as two to three years. The E.U. rules relating to marketing authorizations permit, in exceptional circumstances, the regulatory authorities to grant a marketing authorization where the applicant is not able to provide the usual comprehensive set of data relating to safety and efficacy, because the targeted disease state is rarely encountered or because there is a lack of scientific knowledge about the disease, or because it would be unethical to collect such data. Marketing authorizations granted on an exceptional circumstances basis are normally subject to the holder fulfilling certain obligations, such as completion by the applicant of particular clinical studies.

In many markets outside of the U.S., regulations exist that permit patients to gain access to unlicensed pharmaceuticals, particularly for severely ill patients where other treatment options are limited or non-existent. Generally, the supply of pharmaceuticals under these circumstances is termed compassionate use or named patient supply. In the E.U., each member state has developed its own system under an E.U. directive that permits the exemption from traditional pharmaceutical regulation of medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility. Essentially, two systems operate among E.U. member states: approval can be given for cohort supply, meaning more than one patient can be supplied in accordance with an agreed treatment protocol; or,

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alternatively, as is the case in the majority of E.U. member states, supply is provided on an individual patient basis. Some countries, such as France, have developed other systems, where an ATU involves a thorough review and approval by the regulator of a regulatory data package. In France, the company then receives an approval to supply. All E.U. member states require assurance of the quality of the product, which is usually achieved by provision of good manufacturing practice, or GMP, certification. In the majority of markets, the prescribing physician is responsible for the use for the product and in some countries the physician in conjunction with the pharmacist must request approval from the regulator to use the unlicensed pharmaceutical. Outside of the E.U., many countries have developed named patient systems similar to those prevalent in Europe.

The U.S., the E.U. and Australia may grant orphan drug designation to drugs intended to treat a rare disease or condition, which, in the U.S., is generally a disease or condition that affects no more than 75 in 100,000 persons or fewer than 200,000 individuals. In the E.U., orphan drug designation can be granted if: the disease affects no more than 50 in 100,000 persons in the E.U. or the drug is intended for a life-threatening, seriously debilitating or serious and chronic condition; without incentive it is unlikely that the drug would generate sufficient return to justify the necessary investment; and no satisfactory method of treatment for the condition exists or, if it does, the new drug will provide a significant benefit to those affected by the condition. In Australia, orphan drug designation can be granted to drugs intended to treat a disease that affects no more than 11 in 100,000 persons or fewer than 2,000 individuals. If a product that has an orphan drug designation subsequently receives the first regulatory approval for the indication for which it has such designation, the product is entitled to orphan exclusivity, meaning that the applicable regulatory authority may not approve any other applications to market the same drug for the same indication, except in certain very limited circumstances, for a period of seven years in the U.S., ten years in the E.U. and five years in Australia. Orphan drug designation does not prevent competitors from developing or marketing different drugs for an indication. Orphan drug designation must be requested before submitting an NDA or MAA. After orphan drug designation is granted, the identity of the therapeutic agent and its potential orphan use are publicly disclosed. Orphan drug designation does not convey an advantage in, or shorten the duration of, the review and approval process.

For both currently marketed and future products, failure to comply with applicable regulatory requirements after obtaining regulatory approval can, among other things, result in the suspension of regulatory approval, as well as possible civil and criminal sanctions. Renewals in Europe may require additional data, which may result in a license being withdrawn. In the U.S. and the E.U., regulators have the authority to revoke, suspend or withdraw approvals of previously approved products, to prevent companies and individuals from participating in the drug-approval process, to request recalls, to seize violative products and to obtain injunctions to close manufacturing plants not operating in conformity with regulatory requirements and to stop shipments of violative products. In addition, changes in regulation could harm our financial condition and results of operation.

Product Regulation

We are also subject to various federal and state laws pertaining to health care fraud and abuse, including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment to third party payors (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services.

As a drug marketer, we participate in the Medicaid rebate program established by the Omnibus Budget Reconciliation Act of 1990, and under amendments of that law that became effective in 1993. Participation in this program includes requirements such as extending comparable discounts under the Public Health Service, or PHS, pharmaceutical pricing program. Under the Medicaid rebate program, we pay a rebate for each unit of our product reimbursed by Medicaid. The amount of the rebate for each product is set by law as a minimum 15.1% of the average manufacturer price, or AMP, of that product, or if it is greater, the difference

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between AMP and the best price available from us to any customer. The rebate amount also includes an inflation adjustment if AMP increases faster than inflation. The PHS pricing program extends discounts comparable to the Medicaid rebate to a variety of community health clinics and other entities that receive health services grants from the PHS, as well as hospitals that serve a disproportionate share of poor Medicare and Medicaid beneficiaries. The rebate amount is recomputed each quarter based on our reports of our current average manufacturer price and best price for each of our products to the Health Care Financing Administration.

As a result of the Veterans Health Care Act of 1992, federal law requires that product prices for purchases by the Veterans Administration, the Department of Defense, Coast Guard, and the PHS (including the Indian Health Service) be discounted by a minimum of 24% off the AMP to non-federal customers, the non-federal average manufacturer price, or non-FAMP. Our computation and report of non-FAMP is used in establishing the price, and the accuracy of the reported non-FAMP may be audited by the government under applicable federal procurement laws.

Under the laws of the U.S., the member states of the E.U. and other countries, we and the institutions where we sponsor research are subject to certain obligations to ensure the protection of personal information of human subjects participating in our clinical trials. We have instituted procedures that we believe will enable us to comply with these requirements and the contractual requirements of our data sources. The laws and regulations in this area are evolving and further regulation, if adopted, could affect the timing and the cost of future clinical development activities.

We are subject to the U.S. Foreign Corrupt Practices Act which prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. Under this act, it is illegal to pay, offer to pay, or authorize the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise i