Gentium S.p.A.
Form 20-F
March 31, 2009

As filed with the Securities and Exchange Commission on March 31, 2009

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 20-F

o REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934

OR

þ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the Fiscal Year Ended: December 31, 2008

OR

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

OR

o SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

000-51341
(Commission file number)

GENTIUM S.p.A.
(Exact Name of Registrant as Specified in its Charter)
NOT APPLICABLE
(Translation of Registrant's Name into English)

Italy

(Jurisdiction of incorporation or organization)

Piazza XX Settembre 2
22079 Villa Guardia (Como), Italy
+39 031 385111
(Address, including zip code, and telephone number,
including area code, of Registrant's principal executive offices)

Securities registered or to be registered pursuant to Section 12(b) of the Act.

Title of each class	Name of each exchange on which registered
American Depositary Shares	The Nasdaq Global Market
Ordinary shares with a par value of €1.00 each*	The Nasdaq Global Market

(Title of Class)

Securities registered or to be registered pursuant to Section 12(g) of the Act: None

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act: None

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the annual report.

14,956,317 ordinary shares

- Not for trading, but only in connection with the registration of the American Depositary Shares.

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

Yes o No þ

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934.

Yes o No þ

Note – Checking the box above will not relieve any registrant required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 from their obligations under those Sections.

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 whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o Accelerated filer o Non-accelerated filer þ

Indicate by check mark which financial statement item the registrant has elected to follow.

Item 17 o Item 18 þ

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes o No þ

Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court.

Not applicable.

TABLE OF CONTENTS

PART I

ITEM 1. IDENTITY OF DIRECTORS, SENIOR MANAGEMENT AND ADVISORS

Not applicable.

ITEM 2. OFFER STATISTICS AND EXPECTED TIMETABLE

Not applicable.

ITEM 3. KEY INFORMATION

GENTIUM S.P.A.

We are a biopharmaceutical company focused on the development and manufacture of defibrotide, a DNA based drug derived from pig intestines, to treat and prevent a disease called hepatic veno-occlusive disease, or VOD, a condition in which some of the veins in the liver are blocked as a result of cancer treatments such as chemotherapy or radiation treatments that are given prior to stem cell transplantation. Severe VOD is the most extreme form of VOD and is associated with multiple-organ failure. We are concluding a Phase III clinical trial of defibrotide to treat severe VOD in the United States, Canada and Israel, but do not believe that this current Phase III clinical trial will produce sufficient data to obtain regulatory approval in the United States or Europe; however we do expect to utilize this data as supportive data for future clinical trials. We are also conducting a Phase II/III clinical trial of defibrotide in Europe to prevent VOD in children, which we believe could provide contingent regulatory approval in Europe upon positive data. We are currently working on a revised strategy with our commercial partner regarding the treatment indication of defibrotide.

We have a plant in Italy where we manufacture active pharmaceutical ingredients, which are used to make the finished forms of various drugs. One of those active pharmaceutical ingredients is defibrotide. The other active pharmaceutical ingredients that we manufacture for sale are urokinase, calcium heparin, sodium heparin and sulglicotide. We sell these other active pharmaceutical ingredients to other companies to be made into various drugs. All of the Company's operating assets are located in Italy.

We have prepared our financial statements assuming that we will continue as a going concern, which contemplates realization of assets and satisfaction of liabilities in the normal course of business. We have accumulated a deficit of €95.11 million since inception and expect to continue to incur net operating losses for the foreseeable future and may never become profitable. We have not generated any revenues from our primary product candidate, other than for limited use in Italy, and are dependent upon significant financing or alternative funding to provide the working capital necessary to execute our business plan. We currently anticipate that our cash and cash equivalents as of December 31, 2008 are sufficient to meet our anticipated working capital and operating needs through August of 2009. Accordingly, if we do not obtain sufficient funding in the near future, we will not be able to continue as a going concern.

SELECTED FINANCIAL DATA

The following selected financial data should be read in conjunction with "Operating and Financial Review and Prospects" and our financial statements and the related notes appearing elsewhere in this annual report. The selected financial data as of December 31, 2007 and December 31, 2008 and for each of the three years ended December 31, 2008 are derived from our audited financial statements, which are included in this annual report. The selected financial data as of December 31, 2004, December 31, 2005 and December 31, 2006 and for the years ended December 31, 2004 and December 31, 2005 has been derived from our audited financial statements, which are not included in this annual report. Our historical results are not necessarily indicative of results to be expected in any future period.

Certain reclassification of prior period amounts have been made to our financial statements to conform to the current period presentation. The convenience translation into U.S. dollars has been done solely for the benefit of the reader, and does not imply that our results would actually have been these amounts in U.S. dollars had the U.S. dollar been our functional currency.

Statement of Operations Data: (000s omitted except per share data)	For the Years Ended December 31,					
	2004	2005	2006	2007	2008	2008(1)
Revenues:						
Product sales to related party	€ 2,870	€ 3,260	€ 3,754	€ 2,704	€ 651	$ 906
Product sales to third parties	243	101	321	2,390	4,792	6,670
Total product sales	3,113	3,361	4,075	5,094	5,443	7,576
Other revenue	583	280	249	2,515	1,995	2,777
Total revenues	3,696	3,641	4,324	7,609	7,438	10,353
Operating costs and expenses:						
Cost of goods sold	2,579	2,911	3,092	4,584	5,596	7,789
Charges from related parties	1,665	1,047	854	748	537	747
Research and development	2,922	4,557	8,927	14,497	9,569	13,319
General and administrative	1,194	2,284	5,421	6,279	7,668	10,673
Depreciation and amortization	89	118	261	725	998	1,389
Write-down of assets	-	-	-	13,740	3,403	4,737
	8,449	10,917	18,555	40,573	27, 771	38,654
Operating loss	(4,753)	(7,276)	(14,231)	(32,964)	(20,333)	(28,302)
Foreign currency exchange gain (loss), net	(55)	(249)	(627)	(4,001)	173	241
Interest income (expense), net	(2,192)	(4,148)	490	1,357	256	356

Pre-tax income loss		(7,000)		(11,673)		(14,368)		(35,608)		(19,904)		(27,704)
Income tax expense (benefit):												
Current		65		-		-		-		-		-
Deferred		(37)		646		-		-		-		-
		28		646		-		-		-		-
Net loss	€	(7,028)	€	(12,319)	€	(14,368)	€	(35,608)	€	(19,904)	$	(27,704)
Net loss per share:												
Basic and Diluted	€	(1.41)	€	(1.78)	€	(1.33)	€	(2.52)	€	(1.33)	$	(1.85)

(1) Euro amounts are translated into U.S. dollars using the Noon Buying Rate for the Euro on December 31, 2008, of US$1.3919 per Euro. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

The following table summarizes certain of our balance sheet data.

(000s omitted except per share data	2004	2005	2006	2007	2008	2008(1)
Balance Sheet Data:						
Cash and cash equivalents	€ 2,461	€ 12,785	€ 10,205	€ 25,964	€ 11,491	$ 15,994
Working capital (deficit)	(7,611)	11,758	13,543	19,002	3,152	4,387
Property, net	8,543	8,631	9,424	11,544	10,751	14,964
Total assets	15,909	26,113	35,393	51,959	26,901	37,444
Long-term debt, net of current maturities	3,361	2,485	5,683	4,421	3.268	4,549
Shareholders' equity (deficit)	(2,074)	17,474	21,687	28,359	10,451	14,547
Capital stock	€ 5,000	€ 9,611	€ 11,774	€ 14,946	€ 14,956	$ 20,817
Number of shares	5,000,000	9,610,630	11,773,613	14,946,317	14,956,317	14,956,317

(1) Euro amounts are translated into U.S. dollars using the Noon Buying Rate for the Euro on December 31, 2008, of US$1.3919 per Euro. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

Exchange Rate Information

Fluctuations in the exchange rates between the Euro and the U.S. dollar will affect the U.S. dollar amounts received by owners of ADSs on conversion by the depositary of dividends, if any, paid in euros on the ordinary shares represented by the ADSs. Moreover, such fluctuations may also affect the U.S. dollar price of the ADSs on the Nasdaq Global Market. The following table sets forth information regarding the exchange rates of U.S. dollars per Euro for the periods indicated, calculated by using the average of the noon buying rates on the last day of each month during the periods presented.

	U.S. Dollar per Euro	
Year	Average	Period End
2004	1.2478	1.3538
2005	1.2400	1.1842
2006	1.2661	1.3197
2007	1.3797	1.4603
2008	1.4695	1.3919

Source: Federal Reserve Statistical Releases H.10 and G.5

The following table sets forth information regarding the high and low exchange rates of U.S. dollars per Euro for the periods indicated using the noon buying rate on each day of such period.

	U.S. Dollar per Euro	
Month	High	Low
September 2008	1.4737	1.3939
October 2008	1.4058	1.2446
November 2008	1.3039	1.2525
December 2008	1.4358	1.2634

January 2009	1.3946	1.2804
February 2009	1.3064	1.2547
March 2009 (through March 27, 2009)	1.3730	1.2549

Source: Federal Reserve Statistical Release H.10

On March 27, 2009, the noon buying rate was €1.00 to $1.3306.

We use the Euro as our functional currency for financial reporting. This annual report contains translations of euros into U.S. dollars at specified rates solely for the convenience of the reader. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

CAPITALIZATION AND INDEBTEDNESS

Not applicable.

REASONS FOR THE OFFER AND USE OF PROCEEDS

Not applicable.

RISK FACTORS

You should carefully consider the risks described below, in conjunction with the other information and financial statements and related notes included elsewhere in this annual report, before making an investment decision. You should pay particular attention to the fact that we conduct our operations in Italy and are governed by a legal and regulatory environment that in some respects differs significantly from the environment that prevails in other countries with which you may be familiar. Our business, financial condition or results of operations could be affected materially and adversely by any or all of these risks. In that event, the market price of our ADSs could decline and you could lose all or part of your investment.

Risks Relating to Our Business

We may not be able to meet our cash requirements beyond August of 2009 without obtaining additional capital from external sources, and if we are unable to do so, we may not be able to continue as a going concern.

As of December 31, 2008, we had €11.49 million in cash and cash equivalents. Subsequent to December 31, 2008, we made a final installment payment of €4 million to Crinos S.p.A. related to the acquisition of marketing authorizations and trademarks for Prociclide and Noravid (both forms of defibrotide). As of the date of this report, we anticipate that our current cash will meet our cash requirements through August of 2009. However, in order for us to continue as a going concern beyond this point, we will need to obtain capital from external sources.

We have generated net losses since our inception. Our net losses for the year ended December 31, 2008 and for the year ended December 31, 2007 were €19.90 million and €35.61 million, respectively. We will not be able to continue as a going concern without additional financing. Even if we do raise sufficient capital to support our operating expenses beyond August 2009, there can be no assurances that the proceeds raised will be sufficient to enable us to develop our business to a level where it will generate profits and cash flows from operations. We expect to incur significant losses over the next several years as we conclude our clinical trials, begin new clinical trials, apply for regulatory approvals, continue to develop defibrotide, and pursue commercialization efforts and related activities. Our long-term ability to generate cash from operations is dependent in part on the success of our current strategic partner, Sigma-Tau Pharmaceuticals, Inc., as well as the likelihood and timing of new strategic licensing and partnering relationships and/or successful commercialization of defibrotide. If we incur operating losses for longer than we expect and/or we are unable to raise additional capital, we may become insolvent and unable to continue our operations.

Since our inception, we have financed our operations primarily through the sale of equity and convertible notes, interest income earned on cash and cash equivalents, and debt provided through secured lines of credit. If we raise additional funds through the issuance of equity or convertible debt securities, the percentage ownership of our stockholders could be significantly diluted, and these newly-issued securities may have rights, preferences or privileges senior to those of existing stockholders. If we obtain additional debt financing, a substantial portion of our operating cash flow may be dedicated to the payment of principal and interest on such indebtedness, and the terms of the debt securities issued could impose significant restrictions on our operations.

We have received a report from Reconta Ernst & Young S.p.A. (the Italian affiliate of Ernst & Young LLP), our independent registered public accounting firm, regarding our US GAAP financial statements as of December 31, 2008 and for the fiscal year then ended, which included an explanatory paragraph stating that our recurring operating losses and need for additional financing have raised substantial doubt about our ability to continue as a going concern. This going concern explanatory paragraph included in our auditor's report could inhibit our ability to enter into strategic alliances or our ability to raise additional capital.

Many economists are now predicting that the global economy may face a prolonged recession as a result of the deterioration in the credit markets and related financial crisis, as well as a variety of other factors. While the ultimate

outcome of these events cannot be predicted, they may have a material adverse effect on our liquidity and financial condition if our ability to raise additional funds were to be impaired. The ability of potential patients and/or healthcare payers to pay for defibrotide treatments could also be adversely impacted, thereby limiting our potential revenue. In addition, any negative impacts on our collaborative partners could limit potential revenue from defibrotide.

We had a material weakness in our internal controls over financial reporting as of December 31, 2008.

In connection with the audit of our financial statements for the fiscal year ended December 31, 2008, a material weakness in our internal controls over financial reporting was discovered. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the company's annual or interim financial statements will not be prevented or detected on a timely basis.

The material weakness related to the operation of controls to review and approve the accounting for certain non-routine and estimation processes. As a result, material adjustments to several of our significant accounts and financial statement disclosures, including intangible assets, accounts receivable from related parties, other assets, and operating expenses, were required.

We will take steps to address the material weakness, which we believe will require management's review of non-routine transactions earlier in the process of closing our books.

Our failure to raise additional funds in the future may delay the development of defibrotide.

The development and approval of defibrotide will require a commitment of substantial funds. We are attempting to raise additional funds in advance of depleting our current funds. For the year ended December 31, 2008, our average monthly cash used in operating activities was €1.06 million. Capital expenditures for year ended December 31, 2008 was €0.44 million. You should review the additional information about our liquidity and capital resources in the Operating and Financial Review and Prospects section of this annual report.

Our future capital requirements are dependent upon many factors, some of which are beyond our control, including:

- the successful and continued development of defibrotide in preclinical and clinical testing;
- the costs associated with protecting and expanding our patent and other intellectual property rights;
- future payments, if any, received or made under existing or possible future collaborative arrangements;
- the costs associated with building a future commercial infrastructure;
- the costs associated with implementing any upgrades to our manufacturing facility required by the UnitedStates Food and Drug Administration, or FDA, European Medicines Agency, or EMEA, or other regulators;
- the timing of regulatory approvals needed to market defibrotide; and
- market acceptance of defibrotide.

We will need additional funds before we have completed the development of defibrotide. We cannot assure you that funds will be available to us in the future on favorable terms, if at all. If adequate funds are not available to us on terms that we find acceptable, or at all, we may be required to delay, reduce the scope of, or eliminate research and development efforts or clinical trials on defibrotide. We may also be forced to curtail, cease or restructure our operations, obtain funds by entering into arrangements with collaborators on unattractive terms or relinquish rights to defibrotide that we would not otherwise relinquish in order to continue independent operations.

We have generated limited revenues from commercial sales of our products to date and have had significant losses in recent years and we do not know whether we will ever generate significant revenues or achieve profitability.

We are focused on product development and have generated limited revenues from commercial sales of our products to date. We had total product sales of €4.08 million, €5.09 million and €5.44 million, in 2006, 2007 and 2008, respectively. Even if we are successful selling defibrotide, we may have very limited markets and may not generate enough revenues from defibrotide to fund our business. The FDA and EMEA have designated defibrotide to treat VOD and defibrotide to prevent VOD, as "orphan drugs," which generally means that fewer than 200,000 people are affected by the disease or condition.

We expect to continue to incur significant expenses as we develop and seek regulatory approval for defibrotide. We incurred a net loss of €14.37 million, €35.61 million and €19.90 million in 2006, 2007 and 2008, respectively. We cannot assure you that we will ever become profitable. If we fail to achieve profitability within the time frame expected by investors or securities analysts, the market price of our American Depositary Shares ("ADSs") may decline.

We currently do not have any regulatory approvals to sell defibrotide to treat or prevent VOD, and we cannot guarantee that we will ever be able to sell defibrotide to treat or prevent VOD anywhere in the world.

We must demonstrate that defibrotide satisfies rigorous standards of safety and effectiveness before the FDA, EMEA and other regulatory authorities will approve defibrotide for commercial marketing. We or others must conduct clinical trials of defibrotide, which must be approved by the FDA or other regulatory agencies. These trials are time-consuming and expensive, and we cannot guarantee whether they will be successful. We do not have approval to sell defibrotide to treat or prevent VOD. We will need to conduct significant additional research, preclinical testing and clinical testing before we can file applications with the FDA, EMEA and other regulatory authorities for approval defibrotide. As a result, we may not be able to sell defibrotide anywhere in the world.

The FDA and other regulatory authorities may require us to conduct other clinical trials of defibrotide to treat severe VOD or prevent VOD.

The Dana-Farber Cancer Institute at Harvard University conducted a Phase II clinical trial in the United States for the use of defibrotide to treat severe VOD that concluded in December 2005. Based upon a historical study conducted by Dana-Farber at three centers consisting of 38 patients, we believe that, without treatment, the complete response rate within 100 days after stem cell transplantation is approximately 11% and the survival rate for this disease is approximately 20% after 100 days. As a result of this research and belief and the fact that we believe that there are no approved treatments available at this time, the Dana-Farber clinical investigators did not establish a control group of patients who do not receive the drug, as is customarily done in the FDA approval process, on the basis that it would be unethical to refuse treatment to patients when the treatment being investigated could potentially save their lives. The FDA has stated a preference for a study that utilizes a concurrent control group of untreated patients, but indicated that they would review a trial using a historical control group of untreated patients only. Our current Phase III clinical trial of defibrotide to treat severe VOD used a separate historical control group of untreated patients only.

We do not believe that our current Phase III clinical trial of defibrotide to treat severe VOD will produce sufficient data to obtain regulatory approval in the United States or Europe; however we do expect to utilize this data as supportive data for future clinical trials. We will likely have to conduct a new clinical trial of defibrotide to treat VOD using a concurrent control group of untreated patients. We currently do not, and we may never, have enough capital to commence and complete a new clinical trial of defibrotide to treat severe VOD. In addition, even if we commence a new clinical trial, one or more clinical centers where the clinical trial is to be conducted may not be willing to conduct such a clinical trial on the basis that it is unethical to refuse treatment to patients when the treatment being investigated could potentially save their lives. The committee of clinical investigators who sponsored a Phase II/III clinical trial of defibrotide to treat VOD in Europe conducted by Consorzio Mario Negri Sud, which had a concurrent control group of untreated patients, cancelled the trial in October 2005 due to a lack of patients enrolling. We believe that patients were reluctant to enroll due to the possibility of being placed into the control group and not receiving treatment. Therefore, we may never be able to obtain regulatory approval of defibrotide to treat VOD.

In January 2009, we completed enrollment of our Phase II/III clinical trial of defibrotide to prevent VOD in children in Europe. While EMEA may eventually grant us approval for this indication in Europe, and any such approval may be conditioned upon running an additional trial, which we may not be able to fund. In addition, the FDA may require us to provide sufficient data on our treatment indication to support approval for our prevention indication. Our current Phase III trial is not likely to produce sufficient data to support approval in the United States for our prevention indication and we may not be able to commence and complete a new trial for the treatment of VOD. Accordingly, we may not be able to obtain US regulatory approval of defibrotide to prevent VOD.

We may be required to suspend or discontinue clinical trials due to adverse events or other safety issues that could preclude approval of defibrotide.

Our clinical trials may be suspended at any time for a number of safety-related reasons. For example, we may voluntarily suspend or terminate our clinical trials if at any time we believe that defibrotide prevents an unacceptable risk to the clinical trial patients. In addition, institutional review boards or regulatory agencies may order the temporary or permanent discontinuation of our clinical trials at any time if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements, including if they present an unacceptable safety risk to patients.

Administering any product candidate to humans may produce undesirable side effects. VOD is a complication associated with high dose chemotherapy and stem cell transplantation. Adverse events involving vascular disorders, coagulation, and potentially life-threatening bleeding have been reported in patients with VOD treated with

defibrotide which potentially could be related to the defibrotide therapy. Hypotension has been reported as a possibly related serious adverse event in the trials of defibrotide to treat severe VOD. Also, we discontinued a 69-patient Phase I/II clinical trial of defibrotide to prevent deep vein thrombosis after hip surgery in Denmark in 2002 after three patients experienced hypotension after receiving the defibrotide intravenously. That trial was discontinued due to the hypotension and because defibrotide can also be administered orally to prevent deep vein thrombosis. These adverse events reports will be weighed by the FDA and other regulatory authorities in determining whether defibrotide can, from a risk-benefit perspective, be considered to be safe and effective to treat severe VOD, to prevent deep vein thrombosis or any other indication for which approval is sought.

It is possible that as further data are collected and analyzed, additional adverse events or safety issues could emerge which could impact conclusions relating to the safety of defibrotide. Any problems that arise from the use of defibrotide would severely harm our business operations.

We expect to rely upon our affiliates, FinSirton S.p.A. and Sirton Pharmaceuticals S.p.A., for various services, and we may not be able to quickly replace these services if either FinSirton or Sirton, or both, go bankrupt.

We depend on a number of services from Sirton Pharmaceuticals S.p.A., including steam related to our manufacturing plant, and lab space. In addition, we currently rely upon Sirton to fill and finish defibrotide for use in our clinical trials and compassionate use programs. We also lease lab, storage and office space from Sirton's parent company, FinSirton S.p.A. As discussed in the below risk factor, Sirton has not been able to pay its receivable to us. If FinSirton or Sirton, or both, were to go bankrupt or otherwise cease in providing these services, we may not be able to replace these services in a timely manner. Such a delay would impact our clinical trials, compassionate use programs, and impact our revenues.

Sirton, who is our affiliate, owes us a large receivable that we may not be able to collect.

At December 31, 2008, Sirton owed us a receivable of €2.10 million and we owed Sirton a payable of €0.30 million. Sirton has been unable to make timely payments on the outstanding receivables. In 2008, the Company and Sirton formally offset €3.23 million of payables due to Sirton against the same amount of receivables due from Sirton. We may never be able to collect the net receivables due to us from Sirton.

Defibrotide could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements, if and when defibrotide is approved.

Any product for which we obtain marketing approval, together with the manufacturing processes, post-approval commitments, and advertising and promotional activities for such product, will be subject to continued regulation by the FDA and other regulatory agencies. Later discovery of previously unknown problems with defibrotide or its manufacture, or failure to comply with regulatory requirements, may result in:

- restrictions on defibrotide or manufacturing processes;
- withdrawal of defibrotide from the market;
- voluntary or mandatory recalls;
- fines;
- suspension of regulatory approvals;
- product seizures; or
- injunctions or the imposition of civil or criminal penalties.

If we are slow to adapt, or unable to adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements or policies, we may lose marketing approval for defibrotide when and if defibrotide is approved.

Our manufacturing facility and the manufacturing facility of Patheon, who will fill and finish defibrotide, are subject to continuing regulation by Italian authorities and are subject to inspection and regulation by the FDA and EMEA. These authorities could force us to stop manufacturing our products if they determine that we or Patheon are not complying with applicable regulations or require us to complete further costly alterations to our facilities.

We manufacture active pharmaceutical ingredients at our manufacturing facility in Italy. We have hired Patheon to process our lead active pharmaceutical ingredient, defibrotide, into the finished drug at Patheon's manufacturing facility. These facilities are subject to continuing regulation by the Italian Health Authority and other Italian regulatory authorities with respect to manufacturing our current products. The facilities are also subject to inspection and regulation by the FDA and EMEA with respect to manufacturing our product candidates for investigational use. Also, part of the process for obtaining approval from the FDA and EMEA for defibrotide is approval by those authorities of these manufacturing facilities compliance with current good manufacturing practices. After receiving initial approval, if any, the FDA or EMEA will continue to inspect our manufacturing facilities, including inspecting them unannounced, to confirm whether we and Patheon are complying with the good manufacturing practices.

These regulators may require us to stop manufacturing our products and may deny us approval to manufacture our product candidates if they determine that we or Patheon are not complying with applicable regulations. In addition, these regulators may require us to complete costly alterations to our facilities.

We expect to rely upon a sole processor, Patheon Italia S.p.A., to fill and finish defibrotide into marketable formulations, and we may not be able to quickly replace Patheon if it fails in its duties.

We have entered into an agreement with Patheon Italia S.p.A. to fill and finish defibrotide. If Patheon does not or is not able to perform these services for any reason, it may take us time to find a replacement processor. Such a delay could potentially put us in breach of our contractual obligations into which we may enter, violate local laws requiring us to deliver the product to those in need and impact our revenues.

We may have difficulty obtaining raw material for defibrotide.

Defibrotide is based on pig intestines. If our current sources of pig intestines develop safety problems or other issues that impact our supply of pig intestines, we may not be able to find alternative suppliers in a timely fashion. In that case, we would have to slow or cease our manufacture of defibrotide.

If our third-party clinical trial vendors fail to comply with strict regulations, the clinical trials for defibrotide may be delayed or unsuccessful.

We do not have the personnel capacity to conduct or manage all of the clinical trials that we intend for defibrotide. We rely on third parties to assist us in managing, monitoring and conducting our clinical trials. We have entered into and expect to continue to enter into clinical trial agreements with numerous centers in the United States, Canada and Israel regarding our Phase III clinical trial of defibrotide to treat severe VOD. We have entered into a co-sponsoring agreement with the European Group for Blood and Marrow Transplantation, regarding a Phase II/III clinical trial of defibrotide to prevent VOD in children in Europe. We have entered into an agreement with MDS Pharma Services (U.S.) Inc. to perform clinical research services in connection with clinical trials conducted in the United States and agreements with KKS-UKT, GmbH and MDS Pharma Services S.p.A. to provide such services for our clinical trials in Europe. If these third parties fail to comply with applicable regulations or do not adequately fulfill their obligations under the terms of our agreements with them, we may not be able to enter into alternative arrangements without undue delay or additional expenditures and, therefore, the clinical trials for defibrotide may be delayed or unsuccessful.

Furthermore, the FDA can be expected to inspect some or all of the clinical sites participating in our clinical trials, or our third party vendors' sites, to determine if our clinical trials are being conducted according to good clinical practices. If the FDA determines that these clinical sites or our third-party vendors are not in compliance with applicable regulations, we may be required to delay, repeat or terminate the clinical trials. Any delay, repetition or termination of our clinical trials could materially harm our business.

We are currently dependent on third parties to market and distribute defibrotide in finished dosage form, and we may continue to be dependent on third parties to market and distribute defibrotide.

Our internal ability to handle the marketing and distribution functions for defibrotide is limited and we do not expect to develop the capability to provide marketing and distribution for defibrotide. Our long-term strategy includes either developing marketing and distribution capacity internally or entering into alliances with third parties to assist in the marketing and distribution of our product candidates. We have entered into an agreement with Sigma-Tau Pharmaceuticals, Inc. to market defibrotide to treat VOD in North America, Central America and South America and we may need to develop these capabilities internally or enter into similar agreements to market and distribute defibrotide to prevent VOD. We face, and will continue to face, intense competition from other companies for collaborative arrangements with pharmaceutical and biotechnology companies, for establishing relationships with academic and research institutions, for attracting investigators and sites capable of conducting our clinical trials and for licenses of proprietary technology. Moreover, these arrangements are complex to negotiate and time-consuming to document. Our future profitability will depend in large part on our ability to enter into effective marketing agreements and our product revenues will depend on those marketers' efforts, which may not be successful.

If we are unable to attract and retain key personnel, we may be unable to successfully develop and commercialize defibrotide or otherwise manage our business effectively.

We are highly dependent on our senior management, whose services are critical to the successful implementation of our product acquisition, development and regulatory strategies. If we lose their services or the services of one or more of the other members of our senior management or other key employees, our ability to successfully commercialize defibrotide or otherwise manage our business effectively could be seriously harmed.

Replacing key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of specific skills and experience required to develop, gain regulatory approval of and commercialize defibrotide successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel. In addition, under Italian law, we must pay our Italian employees a severance amount based on their salary and years of service if they leave their employment, even if we terminate them for cause or they resign.

In order to expand our operations, we will need to hire additional personnel and add corporate functions that we currently do not have. Our ability to manage our operations and growth will require us to continue to improve our operational, financial and management controls and reporting system and procedures, or contract with third parties to provide these capabilities for us.

All of our manufacturing capability is located in one facility that is vulnerable to natural disasters, telecommunication and information system failures, terrorism and similar problems, and we are not insured for losses caused by all of these incidents.

We conduct all of our manufacturing operations in one facility located in Villa Guardia, near Como, Italy. This facility could be damaged by fire, floods, earthquake, power loss, telecommunication and information system failures, terrorism or similar events. Our insurance covers losses to our facility, including the buildings, machinery, electronic equipment and goods, for approximately €15 million, but does not insure against all of the losses listed above, including terrorism and some types of flooding. Although we believe that our insurance coverage is adequate for our current and proposed operations, there can be no guarantee that it will adequately compensate us for any losses that may occur. We are not insured for business interruption and we have no replacement manufacturing facility readily available.

We have sold Prociclide and Noravid (both forms of defibrotide) in Italy to treat vascular disease with risk of thrombosis, which may affect the pricing of defibrotide for the prevention or treatment of VOD.

Until December 31, 2008, through our distribution agreement with Crinos S.p.A., we sold Prociclide and Noravid (both forms of defibrotide) in Italy to treat vascular disease with risk of thrombosis. While we have stopped selling Prociclide and Noravid for this treatment in Italy, if defibrotide is approved for sale in Europe or Italy to treat and prevent VOD, or both, we may need to also obtain approval from regulators as to what price we can charge for these uses of defibrotide. The regulators may impose an artificially low cap on defibrotide based on the relatively low price-point of Prociclide and Noravid previously sold in Italy for the treatment of vascular disease with risk of thrombosis.

Our industry is highly competitive and subject to rapid technological changes. As a result, we may be unable to compete successfully or to develop innovative products, which could harm our business.

Our industry is highly competitive and subject to significant and rapid technological change as researchers learn more about diseases and develop new technologies and treatments. While we are unaware of any other products or product candidates that treat or prevent VOD, we believe that other companies have products or are currently developing products to treat some of the same disorders and diseases that defibrotide is designed to treat. These companies include Genzyme Corp., Millennium Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Celgene Corp.

Many of these competitors have substantially greater research and development capabilities and experience, and greater manufacturing, marketing and financial resources, than we do. In addition, these companies' products and product candidates are in more advanced stages of development than ours or have been approved for sale by the FDA and other regulatory agencies. As a result, these companies may be able to develop their product candidates faster than we can or establish their products in the market before we can. Their products may also prove to be more effective, safer or less costly than defibrotide, which could hurt our ability to recognize any significant revenues.

In May 2003, the FDA designated defibrotide as an orphan drug to treat VOD. In January 2007, the FDA designated defibrotide as an orphan drug to prevent VOD as well. If the FDA approves the New Drug Applications that we intend to file before approving a New Drug Application filed by anyone else for these uses of defibrotide, the orphan drug status will provide us with limited market exclusivity for seven years from the date of the FDA's approval of our New Drug Application. However, a marketing authorization to another applicant may be granted for the same product if we give our consent to the second applicant, we are unable to supply sufficient quantities of defibrotide, or the second applicant can establish in its application that its product is safer, more effective or otherwise clinically superior to our product. In that case, our product would not have market exclusivity. Additionally, while we are not aware of any other company researching defibrotide for these uses, if another company does develop defibrotide for these uses,

there is no guarantee that the FDA will approve our New Drug Application before approving the other company's defibrotide product for these uses, in which case the first product approved would have market exclusivity and our products would not be eligible for approval until that exclusivity expires.

In July 2004, EMEA designated defibrotide as an orphan medicinal product to both treat and prevent VOD. If the European regulators grant us a marketing authorization for those uses of defibrotide, we will have limited market exclusivity for those uses for ten years after the date of the approval. However, a marketing authorization may be granted to another applicant for the same product if we give our consent to the second applicant, we are unable to supply sufficient quantities of defibrotide, or the second applicant can establish in its application that its product is safer, more effective or otherwise clinically superior to our product. In that case, our product would not have market exclusivity.

If we are unable to adequately protect our intellectual property, our ability to compete could be impaired.

Our long-term success largely depends on our ability to create and market competitive products and to protect those creations. Our pending patent applications, or those we may file in the future, may not result in patents being issued. Until a patent is issued, the claims covered by the patent may be narrowed or removed entirely and, therefore, we may not obtain adequate patent protection. As a result, we may face unanticipated competition, or conclude that without patent rights the risk of bringing products to the market is too great, thus adversely affecting our operating results.

Because of the extensive time required for the development, testing and regulatory review of a product candidate, it is possible that before defibrotide can be approved for sale and commercialized, our relevant patent rights may expire or remain in force for only a short period following commercialization. We have been issued a patent in the U.S. and several other countries which covers the method for determining the biological activity of defibrotide. This patent expires in 2022 in most countries. We believe this to be an important patent because the analytical release of a biological product like defibrotide is a key step in confirming the purity and biological activity of the final product. There may be no opportunities to extend this patent and thereby extend exclusivity related to FDA and EMEA, in which case we could face increased competition for defibrotide. Patent expiration could adversely affect our ability to protect future product development and, consequently, our operating results and financial position. In addition, generic innovators may be able to circumvent this patent and design a novel analytical method for determining the biological activity of defibrotide. In this case, a generic defibrotide could potentially be on the market once the relevant protections offered by our orphan designations end.

We also rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. We intend to eventually license or sell our products in China, South Korea and other countries which do not have the same level of protection of intellectual property rights that exists in the United Sates and Europe. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

Risks Related to Ownership of the American Depositary Shares

Our ADSs have generally had low trading volume, and its public trading price has been volatile.

Between our initial public offering on June 21, 2005 and December 31, 2008, the closing price of our American Depositary Shares, or ADSs, have fluctuated between $.40 and $24.40 per share, with an average daily trading volume for the twelve months ended December 31, 2008 of approximately 49,234 ADSs. The market may experience significant price and volume fluctuations that are often unrelated to the operating performance of individual companies.

In addition to general market volatility, many factors may have a significant adverse effect on the market price of our ADSs, including:

- continuing operating losses, which we expect over the next several years as we continue our development activities;
- announcements of decisions made by regulators;
- results of our preclinical studies and clinical trials;
- announcements of improvements, new commercial products, failures of products, or progress toward commercialization by our competitors or peers;
- developments concerning proprietary rights, including patent and litigation matters;
- publicity regarding actual or potential results with respect to product candidates under development by us or by our competitors;
- regulatory developments; and
- quarterly fluctuations in our financial results.

We may not remain listed on the Nasdaq Global Market.

Between our public offering and May 2006, our ADSs were listed on the American Stock Exchange. Since May 2006, our ADSs have been listed on the Nasdaq Global Market. The Nasdaq Global Market sets forth various requirements that we must meet in order for our ADSs to continue to be listed on the Nasdaq Global Market. Violations of the continued listing requirements include:

- if the closing bid price of our ADSs drops below $1.00 for a period of 30 consecutive trading days;
- if our stockholders' equity falls below $10 million; or
- if we fail to maintain a market value of publicly held securities of at least $5 million for 30 consecutive trading days.

If we violate any of these continued listing requirements, our ADSs could be delisted from the Nasdaq Global Market. The delisting of our ADSs could have negative results, including the potential loss of confidence by suppliers and employees, the loss of institutional investor interest, and fewer business development opportunities.

On October 16, 2008, given the extraordinary market conditions, Nasdaq suspended the enforcement of the rules requiring a minimum $1.00 closing bid price and requiring a minimum market value of publicly held shares for the Nasdaq Global Market. Nasdaq extended the minimum bid price and market value requirements on December 19, 2008 and again on March 23, 2009, so that these requirements do not need to be met until June 20, 2009. However, this suspension does not apply to the stockholders' equity requirement of $10 million.

As of December 31, 2008, our stockholders' equity was approximately $14.55 million. If we fail to meet the stockholders' equity, or fail to meet the minimum bid price and minimum market value requirements after the suspension, we may be delisted from the Nasdaq Global Market.

Our largest shareholders exercise significant control over us, which may make it more difficult for you to elect or replace directors or management and approve or reject mergers and other important corporate events.

Our largest shareholder, FinSirton S.p.A., owned approximately 25% of our outstanding ordinary shares at March 31, 2009. Dr. Laura Ferro, who is our Chief Executive Officer and President and one of our directors, together with members of her family controls FinSirton. In addition, Sigma-Tau Finanziaria S.p.A., along with its affiliates, owns approximately 18% of our outstanding ordinary shares at March 31, 2009. Marco Codella, who is the chief financial officer of Sigma-Tau Finanziaria, serves as a member of our board of directors. Moreover, we have licensed our rights in defibrotide to treat severe VOD to Sigma-Tau Pharmaceuticals, Inc., a wholly owned subsidiary of Sigma-Tau Finanziaria.

Both FinSirton and Sigma-Tau Finanziaria may substantially control the outcome of all matters requiring approval by our shareholders, including the election of directors and the approval of mergers or other important corporate events. They may exercise this ability in a manner that advances their best interests and not necessarily yours. Also, the concentration of our beneficial ownership may have the effect of delaying, deterring or preventing a change in our control, or may discourage bids for the ADSs or our ordinary shares at a premium over the market price of the ADSs. The significant concentration of share ownership may adversely affect the trading price of the ADSs due to investors' perception that conflicts of interest may exist or arise.

As discussed in our risk factor entitled "Our shareholders can prevent us from executing a financing by alleging that our board of directors acted with serious irregularities when approving such financing, because the terms of such financing could harm our company," both FinSirton and Sigma-Tau Finanziaria own enough of our ordinary shares to bring legal action against our board of directors and may be able to prevent us from completing an important corporate event, such as a financing.

If a significant number of ADSs are sold into the market, the market price of the ADSs could significantly decline, even if our business is doing well.

Our outstanding ordinary shares, ordinary shares issuable upon exercise of warrants and ordinary shares issuable upon exercise of options are not subject to lock-up agreements. We have filed registration statements registering the resale of most of our outstanding ordinary shares and related ADSs and all of our ordinary shares and related ADSs issuable upon exercise of our outstanding warrants and options. Such registration and ultimate sale of the securities in the markets may adversely affect the market for the ADSs.

You may not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise your right to vote.

Except as described in this annual report and in the deposit agreement for the ADSs with our depositary, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares evidenced by the ADSs on an individual basis. Holders of the ADSs will have the right to instruct the depositary as their representative to exercise the rights attached to the ordinary shares represented by the ADSs. You may not receive voting materials in time to instruct the depositary to vote, and it is possible that you, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote.

You may not be able to participate in rights offerings and may experience dilution of your holdings as a result.

We may from time to time distribute rights to our shareholders, including rights to acquire our securities. Under our deposit agreement for the ADSs with our depositary, the depositary will not offer those rights to ADS holders unless both the rights and the underlying securities to be distributed to ADS holders are either registered under the Securities Act of 1933, as amended, or exempt from registration under the Securities Act with respect to all holders of ADSs. We are under no obligation to file a registration statement with respect to any such rights or underlying securities or to endeavor to cause such a registration statement to be declared effective. In addition, we may not be able to take advantage of any exemptions from registration under the Securities Act. Accordingly, holders of our ADSs may be unable to participate in our rights offerings and may experience dilution in their holdings as a result.

You may be subject to limitations on transfer of your ADSs.

Your ADSs represented by the ADRs are transferable on the books of the depositary. However, the depositary may close its transfer books at any time or from time to time when it deems expedient in connection with the performance of its duties. In addition, the depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary deem it advisable to do so because of any requirement of law or of any government or governmental body, or under any provision of the deposit agreement, or for any other reason.

Risks Relating to Being an Italian Corporation

The process of seeking to raise additional funds is cumbersome, subject to the verification of an Italian notary public as to compliance with our bylaws and applicable law and may require prior approval of our shareholders at an extraordinary meeting of shareholders.

We are incorporated under the laws of the Republic of Italy. The principal laws and regulations that apply to our operations, those of Italy and the European Union, are different from those of the United States. In order to issue new equity or debt securities convertible into equity, with some exceptions, we must increase our authorized capital. In order to do so, our board must meet and resolve to recommend to our shareholders that they approve an amendment to our bylaws to increase our capital. Our shareholders must then approve that amendment to our bylaws in an extraordinary meeting duly called, upon the favorable vote of the required majority, which may change depending on whether the meeting is held on a first or second call. These meetings take time to call. In addition, an Italian notary public must verify the compliance of the capital increase with our bylaws and applicable Italian law. Further, under Italian law, our existing shareholders and any holders of convertible securities sometimes have preemptive rights to acquire any such shares on the same terms as are approved, concurrently with the new increase of the authorized capital pro rata based on their percentage interests in our company. Also, our shareholders can authorize the board of directors to increase our capital, but the board may exercise such power for only five years. If the authorized capital is not issued by the end of those five years, the authorized capital expires, and our board and shareholders would need to meet again to authorize a new capital increase. Our shareholders authorized our board of directors to increase our capital by up to €90 million of par value for ordinary shares and €10 million for ordinary shares issuable upon conversion of convertible bonds on April 28, 2006.

Italian law provides that any interested person may, for a period of 180 days following the filing of the shareholders' resolution concerning the approval of the capital increase with the Register of Companies, challenge such capital increase if the increase was not in compliance with Italian law. If a shareholders' meeting was not called to approve the capital increase, any interested person may challenge the capital increase for a period of 90 days following the next shareholders' meeting. In addition, once our shareholders authorize a capital increase, we must issue all of those authorized shares before the shareholders may authorize a new capital increase, unless the shareholders vote to cancel the previously authorized shares. These restrictions could limit our ability to issue new equity or convertible debt securities on a timely basis..

Our shareholders can prevent us from executing a financing by alleging that our board of directors acted with serious irregularities when approving such financing, because the terms of such financing could harm our company.

On August 12, 2008, Sigma Tau Finanziaria S.p.A., together with one of its affiliates, filed a claim in the court of Como claiming that our board of directors acted with serious irregularities in violation of their duties as directors when approving a potential financing, because such financing could harm the company. On August 18, 2008, the court of Como issued a temporary order preventing us from moving forward with the potential financing. While this claim was later dismissed for lack of damages, it did, nonetheless, prevent the directors from approving a potential financing. Any group of shareholders constituting at least 10% of our outstanding ordinary shares could bring a

similar action on a future board resolution regarding a financing or other important corporate action, and an Italian court could prevent the transaction from moving forward by issuing an order to that effect.

We are restricted under Italian law as to the amount of debt securities that we may issue relative to our equity.

Italian law provides that we may not issue debt securities for an amount exceeding twice the amount of the sum of the aggregate par value of our ordinary shares (which we call our capital), our legal reserve and any other disposable reserves appearing on our latest Italian GAAP balance sheet approved by our shareholders. The legal reserve is a reserve to which we allocate 5% of our Italian GAAP net income each year until it equals at least 20% of our Italian GAAP capital. One of the other reserves that we maintain on our balance sheet is a “share premium reserve”, meaning amounts paid for our ordinary shares in excess of the par value for such ordinary shares. At December 31, 2008, the sum of our capital, legal reserves and other reserves on our unaudited Italian GAAP balance sheet was €31.51 million. If we issue debt securities in the future, until such debt securities are repaid in full, we may not voluntarily reduce our capital or allocate our reserves (such as by declaring dividends) if it results in the aggregate of the capital and reserves being less than half of the outstanding amount of the debt. If our equity is reduced by losses or otherwise such that the amount of the outstanding debt securities is more than twice the amount of our equity, some legal scholars are of the opinion that the ratio must be restored by a recapitalization of our company. If our equity is reduced, we could recapitalize by issuing new shares or having our shareholders contribute additional capital to our company, although there can be no assurance that we would be able to find purchasers for new shares or that any of our current shareholders would be willing to contribute additional capital.

If we suffer losses that reduce our capital to less than €120 thousand, we would need to either recapitalize, change our form of entity or be liquidated.

Italian law requires us to reduce our shareholders' equity and, in particular, our capital (aggregate par value of our ordinary shares) to reflect on-going losses. We are also required to maintain a minimum capital of €120 thousand. At December 31, 2008, our Italian GAAP capital was approximately €14.96 million. If we suffer losses from operations that reduce our capital to less than €120 thousand, then either we must increase our capital (which we could do by issuing new shares or having our shareholders contribute additional capital to our company) to at least €120 thousand or convert the form of our company into an S.r.l., which has a lower capital requirement of €10 thousand. If we did not take these steps, our company could be liquidated.

We apply our losses from operations against our legal reserves and capital. If our capital is reduced for more than one-third as a result of losses, our board of directors must call a shareholders' meeting as soon as possible. The shareholders must vote to elect to either reduce the legal reserves and capital by the amount of the remaining losses, or to carry the losses forward for up to one year. If the shareholders vote to elect to carry the losses forward up to one year, and at the end of the year, the losses are still more than one-third of the amount of the legal reserves and capital, then we must reduce our legal reserves and capital by the amount of the losses.

Due to the differences between Italian and U.S. law, the depositary (on your behalf) may have fewer rights as a shareholder than you would if you were a shareholder of a U.S. company.

We are incorporated under the laws of the Republic of Italy. As a result, the rights and obligations of our shareholders are governed by Italian law and our bylaws, and are in some ways different from those that apply to U.S. corporations. Some of these differences may result in the depositary (on your behalf) having fewer rights as a shareholder than you would if you were a shareholder of a U.S. corporation. We have presented a detailed comparison of the Italian laws applicable to our company against Delaware law in "Item 10, Additional Information, Comparison of Italian and Delaware Corporate Laws." We compared the Italian laws applicable to our company against Delaware law because Delaware is the most common state of incorporation for U.S. public companies.

Italian labor laws could impair our flexibility to restructure our business.

In Italy, our employees are protected by various laws giving them, through local and central works councils, rights of consultation with respect to specific matters regarding their employers' business and operations, including the downsizing or closure of facilities and employee terminations. These laws and the collective bargaining agreements to which we are subject could impair our flexibility if we need to restructure our business.

FORWARD-LOOKING STATEMENTS

This annual report may contain forward-looking statements that involve substantial risks and uncertainties regarding future events or our future performance. When used in this annual report, the words "anticipate," "believe," "estimate," "may," "intent," "continue," "will," "plan," "intend," and "expect" and similar expressions identify forward-looking statements. should read statements that contain these words carefully because they discuss our future expectations, contain projections of our future results of operations or of our financial condition or state other "forward-looking" information. We believe that it is important to communicate our future expectations to our investors. Although we believe that our expectations reflected in any forward-looking statements are reasonable, these expectations may not be achieved. The factors listed in the section captioned "Risk Factors," as well as any cautionary language included in this annual report or incorporated by reference, provide examples of risks, uncertainties and events that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements. Before you invest in our ordinary shares, you should be aware that the occurrence of the events described in the "Risk Factors" section and elsewhere in this annual report could have a material adverse effect on our business, performance, operating results and financial condition. All subsequent written and oral forward-looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by the cautionary statements set forth in this annual report. Except as required by federal securities laws, we are under no obligation to update any forward-looking statement, whether as a result of new information, future events, or otherwise.

You should rely only on the information contained in this annual report. We have not authorized anyone to provide you with information different from that contained in this annual report. The information contained in this annual report is accurate only as of the date of this annual report.

ITEM 4. INFORMATION ON THE COMPANY

HISTORY AND DEVELOPMENT OF THE COMPANY

We were originally formed in 1993 as Pharma Research S.r.L., an Italian private limited company. In December 2000, we changed from a private limited company to an Italian corporation. In July 2001, we changed our name to Gentium S.p.A. Under our current bylaws, the duration of our company will expire on December 31, 2050. We are governed by the Italian Civil Code.

We were part of a group of pharmaceutical businesses founded in Italy in 1944 that has been involved in the research and development of drugs derived from DNA and DNA molecules since the 1970s. In 1986, our founding company received approval to sell Prociclide and Noravid (both forms of defibrotide) in Italy to treat deep vein thrombosis, and, in 1993, our founding company received approval to manufacture and sell a form of defibrotide in Italy to both treat and prevent all vascular disease with risk of thrombosis. We are currently focused on the development of defibrotide to treat and prevent VOD in the United States and Europe.

In June 2005, we consummated an initial public offering of our ADSs, which began trading on the American Stock Exchange. In May 2006, we transitioned the trading of our ADSs from the American Stock Exchange to the Nasdaq Global Market.

We have Italian, United States and international trademark rights in "Gentium," United States and European Union trademark rights in "Gentide," international and Italian trademark rights in "Oligotide," and Italian trademark rights to "Pharma Research" and "Dinelasi". We also have a number of patent registrations issued and pending in Italy, the United States and other countries. This annual report also refers to brand names, trademarks, service marks, and trade names of other companies and organizations, and these brand names, trademarks, service marks, and trade names are the property of their respective holders.

This annual report contains market data and industry forecasts that were obtained from industry publications and third parties.

Our principal executive offices are located at Piazza XX Settembre 2, 22079 Villa Guardia (Como), Italy. Our telephone number is +39 031 385111. Our website is located at www.gentium.it. The information contained on our website is not part of this annual report. Our registered agent for service of process in New York is CT Corporation System, located at 111 Eighth Avenue, 13th Floor, New York, New York 10011, telephone number (212) 894-8940.

CAPITAL EXPENDITURES

The following table sets forth our capital expenditures for each year in the three-year period ended December 31, 2008.

	For the Year Ended December 31,		
(in thousands)	2006	2007	2008
Land and buildings	€ 7	€ 162	€ 4
Plant and machinery	793	1,839	544
Industrial equipment	254	582	179
Other	108	90	13
Leasehold improvements	46	249	27
Computer Software	259	69	224
Construction in progress	46	250	172
Total	€ 1,513	€ 3,241	€ 1,163

All of these capital expenditures are in Italy. We are financing these expenditures from offerings of our ordinary shares and loans from third parties.

BUSINESS OVERVIEW

We are building upon our extensive experience with defibrotide, a DNA based drug derived from pig intestines, which our founding company discovered over 20 years ago. We are focused on development and manufacture of defibrotide to treat and prevent a disease called hepatic veno-occlusive disease, or VOD, a condition in which some of the veins in the liver are blocked as a result of cancer treatments such as chemotherapy or radiation treatments that are given prior to stem cell transplantation. Severe VOD is the most extreme form of VOD and is associated with multiple-organ failure. We are concluding a Phase III clinical trial of defibrotide to treat severe VOD in the United States, Canada and Israel. In addition, we are conducting a Phase II/III clinical trial of defibrotide in Europe to prevent VOD in children.

A historical study conducted by Harvard University's Dana-Farber Cancer Institution of 38 patients in three clinical centers indicated that, without treatment, only approximately 11% of patients with severe VOD achieved a complete response to the disorder within 100 days of their stem cell transplantation, and only approximately 20% survived 100 days. By comparison, results from a Phase II clinical trial conducted by Dana-Farber of 141 evaluable patients with severe VOD who were treated with defibrotide showed a complete response rate after 100 days of approximately 46% and a survival rate after 100 days of approximately 41%. However, both the historical study and the Phase II clinical trial were based on very few patients and may not accurately show either true complete response and survival rates without treatment or the efficacy of defibrotide. We believe that there is no drug approved by the FDA or European regulators to treat or prevent VOD.

In May 2003, the FDA designated defibrotide as an orphan drug for treatment of VOD. In January 2007, the FDA designated defibrotide as an orphan drug for prevention of VOD. In July 2004, EMEA granted us orphan medicinal product designation for the use of defibrotide to both treat and prevent VOD.

Due to the historically low complete response and survival rates and lack of treatments for VOD, we believe there is an immediate need for a drug to treat and prevent VOD. The FDA has a "fast track" designation program which is designed to facilitate the development and expedite their review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. The FDA has designated defibrotide to treat severe VOD as a fast track product. The FDA approval process for defibrotide for this use remains dependent upon the successful completion a clinical trial to treat severe VOD.

We do not believe that our current Phase III clinical trial to treat severe VOD will provide sufficient data to obtain regulatory approval in the United States or Europe; however we do expect to utilize this data as supportive data for future clinical trials. In addition, we believe that positive data from our current Phase II/III clinical trial in Europe to prevent VOD in children could be considered for contingent regulatory approval in Europe. We need to raise additional funds through debt and/or equity financings, or enter into licensing or similar collaborative arrangements, or both, in addition to the limited cash flow we generate from operations, to complete the development of defibrotide to treat and prevent VOD.

We manufacture defibrotide, calcium heparin, sodium heparin and sulglicotide at our manufacturing facility near Como, Italy, and we lease a facility from one of our affiliates, Sirton, to manufacture urokinase. These products are active pharmaceutical ingredients used to make other drugs. Almost all of our revenues during the past three years have come from sales of these products to Sirton. Our revenues from the sales of these products to date have been generated primarily in Italy and, to a small degree, in South Korea and amounted to €4.1 million, €5.1 million and €5.4 million in 2006, 2007 and 2008, respectively. However, as discussed in our financial statements contained in this report, in 2008, we have not been able to recognize revenue from Sirton due to doubt concerning Sirton's ability to pay its receivable.

Our strategy is to obtain regulatory approval for defibrotide to treat and prevent veno-occlusive disease. Since 2004, we have spent more than €10 million on upgrades to our facilities that we believe will facilitate the FDA and European regulatory approval process for defibrotide and enable our future production. We plan to work with our existing license partner, Sigma-Tau Pharmaceuticals, Inc., and are seeking additional license partners to help with the development and commercialization of defibrotide. We also are attempting to grow our active pharmaceutical ingredient, or API, business through volume and price increases of sulglicotide, urokinase and sodium heparin.

Market Overview

Chemotherapy, radiation therapy and hormone therapy treatments for cancer are used to target and kill cancer cells. In some cases, the therapy treats the cancer directly; in other cases, it is administered to prepare the patient for a stem cell or bone marrow transplant, which treats cancer or other diseases. Unfortunately, these therapies often have significant negative side effects, including damage to the cells that line the blood vessel walls. The damage to these cells can lead to various disorders of the vascular system. Some patients may not be able to continue with cancer treatments because they develop these vascular system complications; other patients considered at high risk of developing these vascular system complications may not receive optimal cancer treatments or any treatment at all.

One of the disorders of the vascular system that can result from chemotherapy, radiation therapy, hormone therapy and stem cell and bone marrow transplants is VOD. These therapies can cause extensive damage to the cells that line the walls of small veins in the liver. The body's natural response is to swell or clot the sites of injury, but this blocks or "occludes" the vein. This blockage of the veins is called "Hepatic Veno-Occlusive Disease," or VOD. VOD can cause damage to the liver and, in its severe form, leads to failure of the liver and other organs (multiple-organ failure), which usually results in death. According to 2003 data from the International Bone Marrow Transplant Registry and the European Bone Marrow Transplant Registry, approximately 21,000 people receive bone marrow transplants, which are types of stem cell transplants, each year in the United States. Based on our review of more than 200 articles in the medical literature, we believe that approximately 12% of patients who undergo stem cell transplants develop VOD. According to a 1998 article in Blood magazine by Enric Carreras et. al., approximately 28% of patients who develop VOD progress to severe VOD. Based upon a historical study conducted by Dana-Farber at three centers consisting of 38 patients, we believe that of the patients who develop severe VOD, only approximately 11% achieve a complete response within 100 days after a stem cell transplantation and only approximately 20% survive more than 100 days. VOD poses a severe risk to the victim's health. We believe that there are no FDA or EMEA approved treatments at this time for VOD.

Strategy

Our strategic objective is to obtain regulatory approval for defibrotide to treat and prevent VOD. We plan to continue to work with our existing license partner, Sigma-Tau Pharmaceuticals, Inc., for the development of defibrotide and commercialization of defibrotide in the Americas. Outside of the Americas, we are seeking additional license partners to help with the development and commercialization of defibrotide. We also are attempting to grow our API business through volume and price increases of sulglicotide, urokinase and sodium heparin.

- Obtain regulatory approval to use defibrotide to treat and prevent VOD. Gentium, as well as independent investigators, have run several studies showing the potential efficacy and safety of defibrotide in the treatment and prevention of VOD (see detail under "Product Candidate" section below). We have received orphan status from both the FDA and EMEA for the use of defibrotide in both the prevention and treatment of VOD. In addition, we have received fast track designation for the use of defibrotide for the treatment of severe VOD prior to stem cell transplantation. The approval of defibrotide for either the treatment or prevention of VOD depends on the success of our ongoing European Phase II/III clinical trial for the prevention of defibrotide in children as well as other confirmatory trials which will likely be required. We also plan to use the results of our current Phase III clinical trial to treat severe VOD, which is in its final stages, as supportive data. It is likely that both the FDA and EMEA will view the results of treatment and prevention trials as supportive of one another, although the exact regulatory approval may include only an indication of prevention, treatment, or both.

- Increase our marketing capacity, including the use of strategic partnerships. We have a strategic license agreement with Sigma-Tau Pharmaceuticals, Inc. to market defibrotide to treat VOD in North America, Central America and South America upon regulatory approval and have granted Sigma-Tau Pharmaceuticals, Inc. a right of first refusal in those territories with respect to offers made by third parties to market defibrotide to prevent VOD. We intend to

develop the capacity to market defibrotide in other jurisdictions and/or pursue similar marketing agreements with other strategic partners for Europe and Asia Pacific.

- Growth of API Business. We currently sell sulglicotide to Samil for use in the South Korean market, urokinase to Crinos for the Italian market and, to a small extent, sodium heparin for use in the Italian market. Our goal is to maximize the utilization of our manufacturing facility and we are exploring ways to increase capacity of heparin and sulglicotide. We are also looking at re-negotiating our existing supply agreements to achieve greater profitability and longer-term commitments.

Product Candidate

The FDA's designation of a product candidate as an orphan drug means that if the FDA approves our New Drug Application for that product candidate before approving a New Drug Application filed by anyone else for that product candidate, we will have limited market exclusivity for that product candidate for seven years from the date of the FDA's approval of our New Drug Application. If the FDA were to approve a New Drug Application filed by someone else for a product candidate prior to the FDA approving our New Drug Application for the product candidate, our ability to market the product candidate would be restricted by their orphan drug exclusivity. Similarly, the Commission of the European Communities designation of a product candidate as an orphan medicinal product means that if the European regulators grant us a marketing authorization for that product candidate, we will have limited market exclusivity for that product candidate for ten years after date of the approval. If the European regulators were to grant a marketing authorization filed by someone else for a product candidate prior to the European regulators granting a marketing authorization for the product candidate, our ability to market the product candidate could be restricted.

Defibrotide to treat severe VOD

In May 2003, the FDA designated defibrotide as an orphan drug to treat VOD. In July 2004, the Commission of the European Communities designated defibrotide to treat VOD as an orphan medicinal product, which is similar to being designated an orphan drug by the FDA.

In 2000, the British Journal of Hematology published the results of a 40 patient "compassionate use" study of defibrotide to treat VOD conducted in 19 centers in Europe from December 1997 to June 1999. Twenty-two patients, or 55%, showed a complete response. Nineteen patients, or 47%, survived more than 100 days after stem cell transplantation. The publication indicated that four patients of the 19 patients who survived more than 100 days subsequently died. Twenty-eight patients were judged likely to die or had evidence of multiple-organ failure. Ten of the 28 "poor risk" patients, or 36%, showed a complete response within 100 days after stem cell transplantation, all of whom also survived for at least 100 days. This publication stated that defibrotide was generally safely administered with no significant side-effects.

In 2002, the results from 88 patients with severe VOD following stem cell transplants who were treated with defibrotide from March 1995 to May 2001 were published in Blood, the Journal of the American Society of Hematology. This publication reported data on 19 patients treated under individual Investigational New Drug Applications and on a subsequent 69 patient multi-center Phase I/II clinical trial that was conducted under an Investigational New Drug Application filed by a Dana-Farber investigator. The primary goal of the trial was the assessment of the potential effectiveness of the drug and its side effects, if any. All patients in the clinical trial received defibrotide on an emergency basis. This publication stated that 32 patients, or 36%, showed a complete response within 100 days after stem cell transplantation, and 31 patients, or 35%, of those patients survived at least 100 days after stem cell transplantation with minimal adverse side effects, primarily transient mild hypotension. Thirteen of those 31 patients who had survived more than 100 days had died by October 2001, the last date for which survival information was available. No mortality from VOD or other toxicity related to the cancer treatment was seen more than 134 days after treatment with defibrotide, with the most common cause of later death being relapse.

In 2004, the results from 45 children and adolescents with VOD following stem cell transplants who were treated with defibrotide were published in Bone Marrow Transplantation. Twenty-two of the 45 patients had severe VOD. Thirty-four of the 45 patients, or 76%, had a complete response within 100 days after stem cell transplantation and 29 patients, or 64%, survived at least 100 days after stem cell transplantation. Of the 22 patients with severe VOD, 11 patients, or 50%, had a complete response and 8 patients, or 36%, survived at least 100 days after stem cell transplantation. The report stated that defibrotide was well tolerated; about one-third of the patients had a form of coagulopathy, and treatment was discontinued in two cases where a severe bleeding disorder was observed, although

the events could not be clearly attributed to defibrotide.

The Dana-Farber investigator also sponsored, under his Investigational New Drug Application, a Phase II clinical trial in the United States of defibrotide which enrolled 150 stem cell transplant patients with severe VOD, of whom 141 were evaluable, at nine cancer centers. This trial was funded by us and $525 thousand in grants from the orphan drug division of the FDA. The purpose of this trial was to evaluate the effectiveness of this drug, including the effect of the drug on the survival rate of patients with severe VOD, the effective dosage and potential adverse side effects. The primary endpoint was complete response, with survival after 100 days as a secondary endpoint. The Dana-Farber investigator presented the results from this Phase II clinical trial at the 47th Annual Meeting of the American Society of Hematology on December 12, 2005. Results show that of 141 patients evaluable for response, 65 patients, or 46%, showed a complete response within 100 days after stem cell transplantation and 62 patients, or 41%, survived at least 100 days after stem cell transplantation, with minimal adverse events. We do not have information about the survival rate after 100 days.

We started a historically controlled Phase III clinical trial in the United States, Canada and Israel for this use in December 2005 in patients with severe VOD. The primary endpoint is complete response within 100 days after stem cell transplantation and the secondary endpoint is survival after 100 days. We do not believe this current Phase III clinical trial will produce sufficient data to obtain regulatory approval in the United States or Europe; however, we believe that the data can be used as supportive data if and when we commence and complete another clinical trial of defibrotide to treat severe VOD. As with our current Phase III trial to treat severe VOD, we will sponsor and conduct any additional clinical trials under our own Investigational New Drug Application that we submitted to the FDA in December 2003. Sponsoring and conducting the additional clinical trials under our own Investigational New Drug Application will allow us to communicate directly with the FDA regarding the development of this drug for marketing approval.

We have also instituted an expanded access program for patients diagnosed with severe VOD in the United States who are not eligible to participate in or otherwise lack access to the Phase III clinical trial. Under an expanded access program, the FDA allows early access to investigational drugs that are being developed to treat serious diseases for which there is no satisfactory alternative therapy. We decided to undertake this expanded access program due to the large numbers of requests for compassionate use Investigational New Drug Application received for the use of defibrotide, and the corresponding burden that sites and investigators have been undergoing to obtain institutional review board and FDA approval for such compassionate use requests. We will collect additional usage tolerability and safety data from these patients to support our planned New Drug Application for this use of defibrotide.

The FDA has designated defibrotide to treat severe VOD occurring after stem cell transplantation by means of injection as a fast track product. The FDA approval process for defibrotide for this use depends upon a properly designed clinical trial and coordination with our corporate partner, Sigma-Tau Finanziaria S.p.A.

Defibrotide to prevent VOD

We believe there is a significant market opportunity for defibrotide to prevent VOD for patients at risk of developing VOD. Based on our experience researching VOD, we believe that many recipients of high doses of chemotherapy, radiation therapy or hormone therapy or of therapies that prepare for stem cell transplants have an elevated risk of developing VOD. In January 2007, the FDA designated defibrotide as an orphan drug to prevent VOD. In July 2004, the Commission of European communities designated defibrotide to prevent VOD, an orphan medicinal product, which is similar to being designated an orphan drug by the FDA. We believe that there are no FDA or European regulatory approved drugs to prevent VOD at this time.

In 2002, the results of a study on defibrotide in patients at high risk of VOD were published in Blood magazine. One of 57 patients who received defibrotide as a preventative agent developed VOD. No patients experienced significant bleeding.

In 2004, results of a study on defibrotide in patients who received chemotherapy and stem cell transplants were published in Blood magazine. Eight of 44 patients, or 18%, who received defibrotide developed VOD, of which three patients, or 7%, developed severe VOD. By comparison, four of 16 control group patients, or 25%, who received heparin instead of defibrotide, developed VOD, of which two, or 12.5%, developed severe VOD. There were no serious adverse events attributed to the use of defibrotide.

In 2006, the results from a preliminary pilot clinical study in Switzerland by the University Hospital of Geneva on defibrotide, in patients at high risk of VOD was published in Blood magazine. The results suggested that defibrotide may provide effective and safe prevention against VOD. The study tested patients who received stem cell transplants. None of the 157 successive transplant patients who received defibrotide as a preventative agent developed VOD. By comparison, 10 of 52 patients who underwent transplants in the same center before the study developed VOD, which was fatal in three cases. The study report indicated that mild to moderate toxicity such as mild nausea, fever and abdominal cramps was documented, although the report stated that it was difficult to determine whether the toxicity was directly attributable to the defibrotide, the chemotherapy that preceded the stem cell transplants or other drugs used during the stem cell transplants. The study report did not indicate the number of patients who experienced this toxicity.

In 2007, the results of a study on defibrotide in patients who received stem cell transplants, a majority of who received reduced intensity cancer treatments but had other risk factors for VOD, were published in Bone Marrow Transplant magazine. None of the 58 patients who received defibrotide as a preventative agent developed VOD. No serious adverse events were reported.

In 2007, the results of a study on defibrotide in patients who received stem cell transplants and had elevated risks for VOD were reported in Blood magazine. One of 39 evaluable patients who received defibrotide as a preventative agent developed VOD. No serious adverse events were reported.

We are co-sponsoring with the European Group for Blood and Marrow Transplantation, a not-for-profit scientific society, a Phase II/III clinical trial in Europe and Israel of defibrotide to prevent VOD in children. Unlike our Phase III treatment trial in the United States, we have a randomized control group of patients who will either receive defibrotide or no treatment.

Current Products

Our current products are all active pharmaceutical product ingredients used to make other drugs. The principal market for most of these products is Italy. We sell one of our active pharmaceutical products, sugligotide, primarily to a company in South Korea. Our products sales to South Korea have been 9.2%, 15%, and 49% of our total product sales for the years 2006, 2007, and 2008, respectively. Our revenues from the sales of all our current products were €4.1 million, €5.1 million, and €5.4 million in 2006, 2007, and 2008, respectively.

Prociclide and Noravid

Historically, we sold defibrotide as an active pharmaceutical ingredient to our affiliate, Sirton, who then used the active pharmaceutical ingredient for defibrotide to fill and finish the product into ampoule and capsule forms. Sirton then sold these forms of defibrotide to Crinos S.p.A., a subsidiary of Stada Arzneimittel AG. Crinos, pursuant to a distribution agreement entered into with us, sold these products throughout Italy, under the trademarks Prociclide and Noravid, to treat and prevent vascular disease with risk of thrombosis.

In 2007, we changed our relationship with Sirton, from customer to a contract manufacturer, and sold the finished forms of Prociclide and Noravid to Crinos directly. On December 31, 2008, the distribution agreement with Crinos expired and, consistent with our overall strategy, we chose not to renew this agreement and discontinued the manufacture of defibrotide to be finished into Prociclide and Noravid. Accordingly, in November 2008, we limited Sirton's manufacturing of defibrotide to uses for our clinical trials and compassionate use programs.

Sulglicotide

Sulglicotide is developed from swine duodenum and appears to have ulcer healing and gastrointestinal protective properties. We sell sulglicotide to Samil, a South Korean company, for use in manufacturing a product of Samil's in South Korea.

Urokinase

Urokinase is made from human urine and has the potential to dissolve fibrin clots and, as such, is used to treat various vascular disorders such as deep vein thrombosis and pulmonary embolisms. We sell urokinase to a number of companies, including Crinos and Sirton.

Seasonality

Seasonality does not affect our business, although the timing of manufacturer orders can cause variability in sales.

Regulatory Matters

Overview

The preclinical and clinical testing, manufacture, labeling, storage, distribution, promotion, sale, import and export, reporting and record-keeping of our product candidates are subject to extensive regulation by governmental authorities in the United States, principally the FDA and corresponding state agencies, and regulatory agencies in foreign countries.

Non-compliance with applicable regulatory requirements can result in, among other things, injunctions, seizure of products, total or partial suspension of product manufacturing and marketing, failure of the government to grant approval, withdrawal of marketing approvals, civil penalty actions and criminal prosecution. Except as discussed

below, we believe that we are in substantial compliance in all material respects with each of the currently applicable laws, rules and regulations mentioned in this section. During the most recent biannual inspection of our manufacturing facility by the Italian Health Authority in February 2007, the Italian Health Authority noted by way of observations certain deficiencies in regard to the operation of our facility. We have corrected all of the deficiencies. Also, a regional Italian regulatory inspector, during an April 2005 inspection of our manufacturing facility, requested that we install an exhaust vent on one of our machines. We have installed this device. In order to obtain FDA approval for the sale of any of our product candidates, the FDA must determine that this facility meets their current good manufacturing practices, or GMP, including requirements for equipment verification and validation of our manufacturing and cleaning processes. The FDA has not yet inspected our facility, but since 2004 we spent over €10 million in upgrades to our facility in anticipation of such an inspection. We are not aware of any other situation that could be characterized as an incidence of non-compliance in the last three years.

United States Regulatory Approval

FDA regulations require us to undertake a long and rigorous process before any of our product candidates may be marketed or sold in the United States. This regulatory process typically includes the following general steps:

- our performance of satisfactory preclinical laboratory and animal studies under the FDA's good laboratory practices regulations;
- our submission to and acceptance by the FDA of an IND which must become effective before human clinical trials may begin in the United States;
- our obtaining the approval of independent Institutional Review Boards at each clinical site to protect the welfare and rights of human subjects in clinical trials;
- our successful completion of a series of adequate and well-controlled human clinical trials to establish the safety, purity, potency and effectiveness of any product candidate for its intended use;
- our submission to, and review and approval by, the FDA of a marketing application prior to any commercial sale or shipment of a product; and
- our development and demonstration of manufacturing processes which conform to FDA-mandated current good manufacturing practices.

This process requires a substantial amount of time and financial resources. In 2002, the FDA announced a reorganization that has resulted in the shift of the oversight and approval process for certain therapeutic biologic drugs and the related staff from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research. Our initial product candidate, defibrotide to treat severe VOD, is being regulated through the latter.

Preclinical Testing

Preclinical tests generally include laboratory evaluation of a product candidate, its chemistry, formulation, stability and toxicity, as well as certain animal studies to assess its potential safety and effectiveness. We must submit the results of these preclinical tests, together with manufacturing information, analytical data and the clinical trial protocol, to the FDA as part of an Investigational New Drug Application, which must become effective before we may begin any human clinical trials. An application automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within this 30-day time period, raises concerns or questions about the intended conduct of the trials and imposes what is referred to as a clinical hold. If one or more of our products is placed on clinical hold, we would be required to resolve any outstanding issues to the satisfaction of the FDA before we could begin clinical trials. Preclinical studies generally take several years to complete, and there is no guarantee that an Investigational New Drug Application based on those studies will become effective, allowing clinical testing to begin.

Clinical Trials

In addition to FDA review of an application, each clinical institution that desires to participate in a proposed clinical trial must have the clinical protocol reviewed and approved by an independent Institutional Review Board. The independent Institutional Review Boards consider, among other things, ethical factors, informed consent and the selection and safety of human subjects. Clinical trials must also be conducted in accordance with the FDA's good clinical practices requirements. Prior to commencement of each clinical trial, the sponsor must submit to the FDA a clinical plan, or protocol, accompanied by the approval of the committee responsible for overseeing clinical trials at one of the clinical trial sites. The FDA, and/or the Institutional Review Board at each institution at which a clinical

trial is being performed, may order the temporary or permanent discontinuation of a clinical trial at any time if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients.

Human clinical trials are typically conducted in three sequential phases that may overlap, including the following:

Phase I

In Phase I clinical trials, a product candidate is typically given to either healthy people or patients with the medical condition for which the new drug is intended to be used. The main purpose of the trial is to assess a product candidate's safety and the ability of the human body to tolerate the product candidate, and may also assess the dosage, absorption, distribution, excretion and metabolism of the product candidate.

Phase II

During Phase II, a product candidate is given to a limited number of patients with the disease or medical condition for which it is intended to be used in order to:

- further identify any possible adverse side effects and safety risks;

- assess the preliminary or potential effectiveness of the product candidate for the specific targeted disease or medical condition; and

- assess dosage tolerance and determine the optimal dose for a Phase III trial.

Phase III

If and when one or more Phase II trials demonstrate that a specific dose or range of doses of a product candidate is likely to be effective and has an acceptable safety profile, one or more Phase III trials are generally undertaken to demonstrate clinical effectiveness and to further test for safety in an expanded patient population with the goal of evaluating the product's efficacy and its overall risk-benefit relationship of the product candidate. The successful demonstration of clinical effectiveness and safety in one or more Phase III trials is typically a prerequisite to the filing of an application for FDA approval of a product candidate.

After approval, the FDA may also require a Phase IV clinical trial to continue to monitor the safety and effectiveness of the product candidate.

The sponsor must submit to the FDA the results of the pre-clinical and clinical trials, together with, among other things, detailed information on the manufacturing and composition of the product, in the form of a New Drug Application or a Biologics License Application. Once the submission has been accepted for filing, the FDA has 180 days to review the application and respond to the applicant. The review process is often significantly extended by FDA requests for additional information or clarification.

Post-Approval Regulations

If a product candidate receives regulatory approval, the approval is typically limited to specific clinical uses. Subsequent discovery of previously unknown problems with a product may result in restrictions on its use or even complete withdrawal of the product from the market. Any FDA-approved products manufactured or distributed by us are subject to continuing regulation by the FDA, including record-keeping requirements and reporting of adverse events or experiences. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and state agencies, and are subject to periodic inspections by the FDA and state agencies for compliance with current good manufacturing practices, or GMPs, which impose rigorous procedural and documentation requirements upon us and our contract manufacturers. Failure to comply with these requirements may result in, among other things, total or partial suspension of production activities, failure of the FDA to grant approval for marketing, and withdrawal, suspension, or revocation of marketing approvals.

If the FDA approves one or more of our product candidates, we and our contract manufacturers must provide certain updated safety and effectiveness information. Product changes, as well as changes in the manufacturing process or facilities where the manufacturing occurs or other post-approval changes, may necessitate additional FDA review and approval. The labeling, advertising, promotion, marketing and distribution of a drug or biologic product also must be in compliance with FDA requirements which include, among others, standards and regulations for direct-to-consumer advertising, communication of information relating to off-label uses, industry sponsored scientific and educational activities and promotional activities involving the Internet. The FDA has very broad enforcement authority, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing a company to correct deviations from regulatory standards and enforcement actions that can include seizures, fines, injunctions and criminal prosecution.

Fast track and orphan drug designation

The FDA has a “fast track” program that provides the potential for expedited review of an application. However, there is no assurance that the FDA will, in fact, accelerate the review process for a fast track product candidate. Fast track status is provided only for new and novel therapies that are intended to treat persons with life-threatening and severely debilitating diseases, where there is a defined unmet medical need, especially where no satisfactory alternative therapy exists or the new therapy is significantly superior to alternative therapies. During the development of product candidates that qualify for this status, the FDA may expedite consultations and reviews of these experimental therapies. The FDA can base approval of a marketing application for a fast track product on an effect on a clinical endpoint, or on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may condition the approval of an application for certain fast track products on additional post-approval studies to validate the surrogate endpoint or confirm the effect on the clinical endpoint. Fast track status also provides the potential for a product candidate to have a “priority review.” A priority review allows for portions of the application to be submitted to the FDA for review prior to the completion of the entire application, which could result in a reduction in the length of time it would otherwise take the FDA to complete its review of the application. Fast track status may be revoked by the FDA at any time if the clinical results of a trial fail to continue to support the assertion that the respective product candidate has the potential to address an unmet medical need. A product approved under a “fast track” designation is subject to expedited withdrawal procedures and to enhanced scrutiny by the FDA of promotional materials.

The FDA may grant orphan drug status to drugs intended to treat a “rare disease or condition,” which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. If and when the FDA grants orphan drug status, the generic name and trade name of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Aside from guidance concerning the non-clinical laboratory studies and clinical investigations necessary for approval of the application, orphan drug status does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The FDA may grant orphan drug designations to multiple competing product candidates targeting the same uses. A product that has been designated as an orphan drug that subsequently receives the first FDA approval for the designated orphan use is entitled to orphan drug exclusivity, which means the FDA may not approve any other applications to market the same drug for the same indication, except in very limited circumstances, for seven years from the date of FDA approval. Orphan drug status may also provide certain tax benefits. Finally, the FDA may fund the development of orphan drugs through its grants program for clinical studies.

The FDA has designated defibrotide as an orphan drug both to treat VOD and to prevent VOD and has provided funding for clinical studies for defibrotide to treat VOD. The FDA has approved the Company's application for "fast track" designation for defibrotide to treat severe VOD occurring after stem cell transplantation by means of injection. If our other product candidates meet the criteria, we may also apply for orphan drug status and fast track status for such products.

Market Exclusivity

In addition to orphan drug exclusivity, a product regulated by the FDA as a "new drug" is potentially entitled to non-patent and/or patent exclusivity under the Federal Food, Drug and Cosmetic Act, or FFDCA, against a third party obtaining an abbreviated approval of a generic product during the exclusivity period. An abbreviated approval allows an applicant to obtain FDA approval without generating, or obtaining a right of reference to, the basic safety and effectiveness data necessary to support the initial approval of the drug product or active ingredient. In the case of a new chemical entity (an active ingredient which has not been previously approved with respect to any drug product) non-patent exclusivity precludes an applicant for abbreviated approval from submitting an abbreviated application until five years after the approval of the new chemical entity. In the case of any drug substance (active ingredient), drug product (formulation and composition) and method of use patents listed with the FDA, patent exclusivity under the FFDCA precludes FDA from granting effective approval of an abbreviated application of a generic product until the relevant patent(s) expire, unless the abbreviated applicant certifies that the relevant listed patents are invalid, not infringed or unenforceable and the NDA/patent holder does not bring an infringement action within 45 days of receipt of notification of the certification or an infringement action is brought within 45 days and a court determines that the relevant patent(s) are invalid, not infringed or unenforceable or 30 months have elapsed without a court decision of infringement.

User Fees

A New Drug Application for a prescription drug product that has been designated as an orphan drug is not subject to the payment of user fees to the FDA unless the application includes an indication other than the orphan indication.

A supplement proposing to include a new indication for a designated orphan disease or condition in an application is also not subject to a user fee if the drug has been designated an orphan drug with regard to the indication proposed in such supplement.

There is no specific exemption for orphan drug products from annual product and establishment fees. However, sponsors of orphan drugs can request a waiver of such fees on hardship or other grounds.

HIPAA

Other federal legislation may affect our ability to obtain certain health information in conjunction with our research activities. The Health Insurance Portability and Accountability Act of 1996, or HIPAA, mandates, among other things, the adoption of standards designed to safeguard the privacy and security of individually identifiable health information. In relevant part, the U.S. Department of Health and Human Services, or HHS, has released two rules to date mandating the use of new standards with respect to such health information. The first rule imposes new standards relating to the privacy of individually identifiable health information. These standards restrict the manner and circumstances under which covered entities may use and disclose protected health information so as to protect the privacy of that information. The second rule released by HHS establishes minimum standards for the security of electronic health information. While we do not believe we are directly regulated as a covered entity under HIPAA, the HIPAA standards impose requirements on covered entities conducting research activities regarding the use and disclosure of individually identifiable health information collected in the course of conducting the research. As a result, unless they meet these HIPAA requirements, covered entities conducting clinical trials for us may not be able

to share with us any results from clinical trials that include such health information.

Foreign Regulatory Approval

Outside of the United States, our ability to market our product candidates will also be contingent upon our receiving marketing authorizations from the appropriate foreign regulatory authorities whether or not FDA approval has been obtained. The foreign regulatory approval process in most industrialized countries generally includes risks that are similar with the FDA approval process we have described herein. The requirements governing conduct of clinical trials and marketing authorizations, and the time required to obtain requisite approvals may vary widely from country to country and differ from that required for FDA approval.

European Union Regulatory Approval

Under the current European Union regulatory system, applications for marketing authorizations may be submitted either under a centralized or decentralized procedure. The centralized procedure (which is compulsory for certain categories of drugs) provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization that is obtained in accordance with the procedure and requirements applicable in the member state concerned may submit an application to the remaining member states. Within 90 days of receiving the applications and assessment report, each member state must decide whether to recognize approval. The mutual recognition process results in separate national marketing authorizations in the reference member state and each concerned member state.

The centralized procedure

An applicant under the centralized procedure must be a person who is domiciled in the European Union or an entity established in the European Union. The applicant must file a preliminary request containing the information regarding the product candidate, including its description and the location of the production plant, as well as the payment of the application fees. The European Agency for the Evaluation of Medicinal Products (a European Union statutory entity) formally evaluates the preliminary request and indicates either an initial approval to review a full application or a rejection. If the European Agency indicates an initial approval to review a full application, the applicant must submit the application to the European Agency. This application must indicate certain specific information regarding the product candidate, including the composition (quality and quantity) of all the substances contained in the product, therapeutic indications and adverse events, modalities of use, the results of physical, chemical, biological and microbiological tests, pharmacological and toxicity tests, clinical tests, a description of production and related control procedures, a summary of the characteristics of the product as required by the European legislation and samples of labels and information to consumers. The applicant must also file copies of marketing authorizations obtained, applications filed and denials received for the same product in other countries, and must prove that the manufacturer of the product candidate is duly authorized to produce it in its country.

The European Agency (through its internal Committee for Proprietary Medicinal Products) examines the documents and information filed and may carry out technical tests regarding the product, request information from the member state concerned with regard to the manufacturer of the product candidate and, when it deems necessary, inspect the manufacturing facility in order to verify that the manufacturing facility is consistent with the specifications of the product candidate, as indicated in the application.

The Committee generates and submits its final opinion to the European Commission, the member states and the applicant. The Commission then issues its decision, which is binding on all member states. However, if the Commission approves the application, member states still have authority to determine the pricing of the product in their territories before it can be actually marketed.

The European Agency may reject the application if the Agency decides that the quality, safety and effectiveness of the product candidate have not been adequately and sufficiently proved by the applicant, or if the information and documents filed are incomplete, or where the labeling and packaging information proposed by the applicant do not comply with the relevant European rules.

The European Agency has also established an accelerated evaluation procedure applying to product candidates aimed at serious diseases or conditions for which no suitable therapy exists, if it is possible to predict a substantial beneficial effect for patients.

The marketing authorization is valid for five years and may be renewed, upon application, for further five year terms. After the issue of the authorization the holder must constantly take into consideration scientific and technical progress so that the product is manufactured and controlled in accordance with scientific methods generally accepted.

We plan to apply for approvals for our product candidates under the centralized procedure. We believe that the centralized procedure will result in a quicker approval of our product candidates than the decentralized procedure due to the fact that we intend to market our product candidates in many European Union member states, rather than just one.

The decentralized procedure

The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization—obtained in accordance with the procedure and requirements applicable in the member state concerned (see the description below for Italy)—may submit an application to the remaining member states. Within 90 days of receiving the applications and assessment report, each member state must decide whether to recognize approval. The mutual recognition process results in separate national marketing authorizations in the reference member state and each concerned member state.

An application under the decentralized procedure begins with the applicant obtaining a national marketing authorization. An example of the process for obtaining a national marketing authorization in Italy is set forth below. The applicant then submits an application for authorization in other member states and the European Agency. If any of the member states refuses to recognize the authorization by the original member state, the matter is deferred to arbitration proceedings, unless the applicant withdraws its request in the member state refusing recognition. The characteristics of the product in the new applications must be identical to those approved in the original member state.

Italian Regulatory Approval

In order to put a medicinal product on the Italian market it is necessary to obtain, alternatively:

- an authorization from the Italian Agency for the Evaluation of Medical Products ("AIFA") (which may be national or by mutual recognition); or

    - an EU authorization granted by European Agency for the Evaluation of Medicinal Products (EMEA).

The marketing authorization is required for all medicines (including generics, homeopathic, radiopharmaceutical products). The procedure for the mutual recognition applies when a product has been already authorized in a member state of the European Union. Decentralized procedure applies when a product is not yet authorized. During a decentralized procedure, the evaluation process involves all the relevant member states of the European Union, of which one member state is chosen to be the state to be referenced for mutual recognition.

An application for marketing authorization in Italy must be filed by the office of AIFA by an applicant established in the European community. The application must contain certain information, including, but not limited to, composition (quality and quantity) of all the substances contained in the product, therapeutic indications and adverse events, modalities of use, the results of physical, chemical, biological and microbiological tests, pharmacological and toxicity tests, pre-clinical tests and clinical trials, a description of production and related control procedures and samples of labels and information to consumers. For generics, a simplified procedure applies, according to which the applicant is exempted from providing the results of pre-clinical tests and clinical trials.

The AIFA may grant or deny the national authorization after a review of the contents of the application, both from a formal and substantial viewpoint. If an authorization is granted, it is valid for an initial period of five years and, upon application, may be renewed for subsequent five year terms. In particular, the AIFA examines the quality, effectiveness and safety of the product. The AIFA may also order further tests prior to granting or denying the authorization regarding the suitability of the production and control methods described in the application. The AIFA may reject the authorization if the ordinary use of the drug has adverse events, the quality and quantity of the ingredients of the drugs do not correspond to the data indicated in the application, there is a lack, either total or partial, of beneficial therapeutic effects or the information and the documents included in the application do not comply with the requirements provided by law. After the AIFA grants a national authorization, the AIFA may temporarily suspend or revoke the authorization if the information disclosed in the relevant application turns out to be incorrect, the drug no longer meets the necessary quality, effectiveness or safety requirements, or adequate production controls have not been carried out.

Clinical Trials

Italy has implemented European legislation regarding good practices in drug clinical trials. As a result, clinical trials are now governed in great detail and failure to comply with these rules means that the results of the trials will not be taken into consideration in evaluating an application for a marketing authorization.

Prior to starting any clinical trial, the organizing and/or financing entity must obtain the approval of the competent health authorities (which vary depending on the type of drug concerned) and obtain the favorable opinion of the competent Ethical Committee, an independent body. Good practice rules include the following principles:

- the predictable risks and inconveniences shall not outweigh the beneficial effects for the person subject to the trials and for the other current and future patients;

- the person participating in the trials must have been duly informed of all the relevant circumstances and in particular of the right to interrupt the experimentation at any time without any prejudicial consequence, and must have given consent after having been properly informed;

- the right of the participants to their physical and mental integrity, as well as their right to privacy, shall be respected;

- the entity organizing the trial must have obtained adequate insurance coverage for any damage that may derive to the participants because of the trial;
- the name of a person to be contacted for any information must be communicated to the participant; and
- the trial must be conducted by suitably qualified medical personnel.

The trial must be constantly monitored, in particular with regard to serious adverse events which are not envisaged in the approved clinical protocol. The principal investigator managing the trial and the sponsor of the trial have information and notification obligations regulated in detail by the relevant authorities. In particular, whenever the safety of the participants is in danger due to unexpected serious adverse events, the sponsor must promptly inform AIFA and the Ethical Committee. Italian legislation provides sanctions (criminal sanctions and administrative fines) in case of violation of specific good practice rules.

Post-approval issues

There are many national legislative instruments (implementing European Union rules) governing controls on drugs in the post-authorization phase. For instance, the holder of the national marketing authorization must promptly record in detail and notify any adverse reaction to the drug of which it becomes aware, regardless of the country where the reaction occurs, also preparing periodic update reports on these adverse events. For these and other purposes, the holder of the authorization must hire and maintain in its organization a person expert in the field and responsible for all drug controlling and reporting activities.

Moreover, any form of information and advertising aimed at promoting the sale of drugs is governed by specific national legislation (also implementing European Union rules), which provides for the requirements and limitations of advertising messages in general, as well as of other particular promotional activities, such as the organization of conferences regarding certain drugs and the distribution of free samples.

The export of drugs from Italy is not subject to authorization (except for plasma and blood-related products), but the import into Italy from non-European Union countries must be authorized by the Ministry of Health, on the basis of the adequacy of the quality controls to be carried out on the imported drugs.

Pediatric Investigation Plan

The pediatric investigation plan, or PIP, is a key element in the European pediatric regulations and came into effect in January 2007. The PIP is a plan for defining the use of a medicinal product across all age groups of the pediatric population and across all indications. The pediatric committee, or PDCO, is a body within EMEA responsible for overseeing the requirements of the pediatric regulation. The PDCO may grant a waiver from using a medicinal product in certain (or all) indications and/or certain (or all) pediatric age groups, and/or a deferral of the start or completion of all or some of the studies in the PIP. If a sponsor complies with a PIP agreed by PDCO, the sponsor may receive a six-month extension on patents covering the product described in the plan, or if the product has been designated an orphan drug by EMEA, an additional two years of market exclusivity, even if a pediatric indication is not approved.