

SKYEPHARMA PLC  
Form 20-F  
June 28, 2004

[QuickLinks](#) -- Click here to rapidly navigate through this document

As filed with the Securities and Exchange Commission on June 28, 2004

---

---

UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 20-F

(Mark One)

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

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)  
OF THE SECURITIES EXCHANGE ACT OF 1934  
For the fiscal year ended: December 31, 2003  
OR

TRANSITION REPORT PURSUANT TO SECTION 13  
OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934  
For the transition period from N/A to N/A

Commission file number: 0-29860

**SKYEPHARMA PLC**

(Exact name of Registrant as specified in its charter)

**England and Wales**

(Jurisdiction of incorporation or organization)

**105 Piccadilly, London W1J 7NJ, England**

(Address of principal executive offices)

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

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

Ordinary shares of 10p each ("ordinary shares") represented by American Depositary Shares ("ADSs")  
quoted on the NASDAQ National Market System, each ADS representing ten ordinary shares.

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 this Annual Report:

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Ordinary shares, nominal value 10p each 618,669,940

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  No

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

Item 17  Item 18

---

---

---

## TABLE OF CONTENTS

	<b>Page</b>
Presentation of Information	3
Statistical Data	3
Forward-Looking Statements	3
Exchange Rate Information	4
<b>Part I</b>	
Item 1: Identity of Directors, Senior Management and Advisers	5
Item 2: Offer Statistics and Expected Timetable	5
Item 3: Key Information	5
Item 4: Information on the Company	20
Item 5: Operating and Financial Review and Prospects	68
Item 6: Directors, Senior Management and Employees	84
Item 7: Major Shareholders and Related Party Transactions	96
Item 8: Financial Information	98
Item 9: The Offer and Listing	99
Item 10: Additional Information	100
Item 11: Quantitative and Qualitative Disclosures about Market Risk	112
Item 12: Description of Securities other than Equity Securities	118
<b>Part II</b>	
Item 13: Defaults, Dividend Arrearages and Delinquencies	119
Item 14: Material Modifications to the Rights of Security Holders and Use of Proceeds	119
Item 15: Controls and Procedures	119
Item 16A: Audit Committee Financial Expert	119
Item 16B: Code of Ethics	119
Item 16C: Principal Accountant Fees and Services	120
Item 16D: Exemptions from the Listing Standards for Audit Committees	120
Item 16E: Purchases of Equity Securities by the Issuer and Affiliated Purchasers	120
<b>Part III</b>	
Item 17: Financial Statements	121

Item 18: Financial Statements

121

2

---

## PRESENTATION OF INFORMATION

In this Annual Report on Form 20-F ("Form 20-F"), the term "ordinary shares" refers to the ordinary shares, nominal value 10 pence each, of SkyePharma PLC ("SkyePharma" or the "Company"), and together with its consolidated subsidiaries, the "Group") and the term "ADSs" refers to American Depositary Shares each representing the right to receive 10 ordinary shares and evidenced by American Depositary Receipts ("ADRs").

The Company publishes its consolidated financial statements expressed in pounds sterling. In this Annual Report, references to "pounds sterling", "£", "pence" or "p" are to the lawful currency of the United Kingdom; references to "U.S. dollars" or "\$" are to the lawful currency of the United States; references to "Euro" or "€" are to the lawful currency of the members of the European Union that have adopted the single European currency; references to "\$ Canadian" or "Cdn\$" are to the lawful currency of Canada, references to "Swiss francs" or "Chf" are to the lawful currency of Switzerland and references to "Swedish Krona" or "SKr" are to the lawful currency of Sweden. Solely for the convenience of the reader, this Annual Report contains translations of certain pound sterling amounts into U.S. dollar amounts at specified rates. Unless otherwise stated, the translations of pounds sterling into U.S. dollars have been made at the noon buying rate in New York City for cable transfers in pounds sterling, as certified for customs purposes by the Federal Reserve Bank of New York (the "Noon Buying Rate"). No representation is made that pounds sterling have been, could have been or could be converted into U.S. dollars at the rates indicated or at any other rate.

The Company prepares its consolidated financial statements in accordance with generally accepted accounting principles in the United Kingdom ("U.K. GAAP"), which differ in certain significant respects from generally accepted accounting principles in the United States ("U.S. GAAP"). For a description of the principal differences between U.K. GAAP and U.S. GAAP as they relate to SkyePharma and a reconciliation to U.S. GAAP of the Company's U.K. GAAP (loss)/profit for the years ended December 31, 2003, 2002 and 2001 and shareholders' funds at December 31, 2003 and 2002, see Note 32 of the Notes to the Consolidated Financial Statements included in Item 18 of this Form 20-F.

## STATISTICAL DATA

Except where otherwise indicated, figures included in this Form 20-F relating to pharmaceutical market sales are obtained from the Company's collaborative partners.

## FORWARD-LOOKING STATEMENTS

This Form 20-F contains certain forward-looking statements as defined in Section 21E of the Securities Exchange Act of 1934 with respect to the financial condition, results of operations and business of the Company and certain of the plans and objectives of the Board of Directors of the Company with respect thereto. Such statements may generally, but not always, be identified by the use of words such as "anticipates", "should", "expects", "estimates", "believes" or similar expressions. Such statements in this Form 20-F include, but are not limited to, statements under the following headings: (1) "Item 4: Information on the Company"; (2) "Item 5: Operating and Financial Review and Prospects"; (3) "Item 8: Financial Information"; and (4) "Item 11: Quantitative and Qualitative Disclosures About Market Risk". Specific risks faced by the Company are described under "Risk Factors" on pages 8 to 19. By their nature, forward-looking statements involve risk and uncertainty, and the factors described in the context of such forward-looking statements in this Form 20-F could cause actual results and developments to differ materially from those expressed in or implied by such forward-looking statements.

**EXCHANGE RATE INFORMATION**

The table below sets forth, for the periods and dates indicated, certain information concerning the Noon Buying Rates for pounds sterling expressed in U.S. dollars per pound. The period average data set forth below is the average of the Noon Buying Rates on the last day of each full month during the period.

Fluctuations in the exchange rate between the pound sterling and the U.S. dollar will affect, among other things, the U.S. dollar equivalent of the pound sterling price of the ordinary shares on the London Stock Exchange ("LSE"), which is likely to affect the market prices of the ADSs in the United States.

	<u>High</u>	<u>Low</u>	<u>Period Average</u>	<u>Period End</u>
1999	1.6765	1.5515	1.6146	1.6150
2000	1.6538	1.3997	1.5156	1.4955
2001	1.5045	1.3730	1.4382	1.4543
2002	1.6095	1.4074	1.5025	1.6095
2003	1.7842	1.5500	1.6450	1.7842
			<u>High</u>	<u>Low</u>
December 2003			1.7842	1.7200
January 2004			1.8511	1.7902
February 2004			1.9045	1.8182
March 2004			1.8680	1.7943
April 2004			1.8564	1.7674
May 2004			1.8369	1.7544

On June 24, 2004 the Noon Buying Rate was \$1.8216 per £1.00.

For a discussion of the impact of exchange rate fluctuations on the Company's operating results, see "Item 5: Operating and Financial Review and Prospects Operating Results".

**PART I**

**Item 1: Identity of Directors, Senior Management and Advisers**

Not applicable

**Item 2: Offer Statistics and Expected Timetable**

Not applicable

**Item 3: Key Information**

**Selected Financial Data**

The selected financial data set forth below for the Company, for the years ended December 31, 2003, 2002, 2001, 2000 and 1999 have been derived from, and should be read in conjunction with, the Company's Consolidated Financial Statements set forth beginning on page F-1. The Consolidated Financial Statements of the Company for the years ended December 31, 2001, 2000 and 1999 have been audited by PricewaterhouseCoopers, independent Chartered Accountants. The Consolidated Financial Statements of the Company for the years ended December 31, 2003 and 2002 have been audited by PricewaterhouseCoopers LLP, independent Chartered Accountants.

The selected financial data has been prepared on the basis of U.K. GAAP, which differs in certain significant respects from U.S. GAAP. A description of these differences and a reconciliation to U.S. GAAP of the Company's U.K. GAAP (loss)/profit for the years ended December 31, 2003, 2002 and 2001 and shareholders' funds at December 31, 2003 and 2002 are set out in Note 32 to the Consolidated Financial Statements.

For exchange rate information, see "Exchange Rate Information" on page 4 of this Form 20-F. Solely for the convenience of the reader, the pound sterling amounts as of and for the year ended December 31, 2003 have been translated into U.S. dollars at the Noon Buying Rate on December 31, 2003 of \$1.7842 per £1.00.

For a discussion of the impact of exchange rate fluctuations on the Company's operating results, see "Item 5: Operating and Financial Review and Prospects - Operating Results".

The following table sets forth selected consolidated financial information as of and for the five years ended December 31, 2003.

## SkyePharma PLC

Year ended December 31,

## Consolidated Income Statement Data

	1999	2000	2001	2002	2003	2003
(in thousands, except per share data)						
<b>U.K. GAAP<sup>(1)</sup></b>						
Turnover <sup>(2)</sup>	£17,739	£24,292	£46,126	£69,573	£53,152	\$94,834
Cost of sales	(14,854)	(15,598)	(18,820)	(24,830)	(29,786)	(53,144)
Gross profit	2,885	8,694	27,306	44,743	23,366	41,690
Selling, marketing & distribution expenses	(3,161)	(3,844)	(4,804)	(4,769)	(4,348)	(7,758)
Administration expenses	(12,584)	(12,630)	(16,025)	(20,192)	(34,143) <sup>(3)</sup>	(60,918) <sup>(3)</sup>
Research and development expenses	(6,728)	(13,104)	(17,918)	(29,285)	(30,520)	(54,454)
Other operating income		2,900	6,342	14,219	6,126	10,930
Group operating (loss)/profit	(19,588)	(17,984)	(5,099)	4,716	(39,519)	(70,510)
Share of operating (loss)/profit in Joint Venture Associated undertaking	(48)		(578)			
Total operating (loss)/profit	(19,636)	(17,984)	(5,677)	4,716	(39,519)	(70,510)
Reversal of provision for loss on disposal of fixed asset investment	381					
(Loss)/profit on ordinary activities before interest and taxation	(19,225)	(17,984)	(5,677)	4,716	(39,519)	(70,510)
Interest receivable	1,364	1,806	1,251	1,081	1,029	1,836
Interest payable	(1,391)	(3,508)	(4,951)	(4,464)	(4,493)	(8,016)
Taxation	(132)	(4)	(75)	(224)	(240)	(428)
Net (loss)/profit <sup>(2)</sup>	£(19,414)	£(19,690)	£(9,452)	£1,109	£(43,223)	\$(77,118)
Basic weighted average number of shares <sup>(4)</sup>	467,214	508,228	526,250	577,018	609,855	609,855
Diluted weighted average number of shares <sup>(4)</sup>	467,214	508,228	526,250	597,095	609,855	609,855
Basic and diluted (loss)/profit per ordinary share <sup>(4)</sup>	(4.2)p	(3.9)p	(1.8)p	0.2p	(7.1)p	\$(0.127)
<b>U.S. GAAP<sup>(1)</sup></b>						
Turnover	£17,739	£24,103	£44,192	£42,586	£66,538	\$118,717
Group operating loss	£(28,440)	£(26,953)	£(27,517)	£(36,205)	£(23,632)	\$(42,164)
Net loss under U.S. GAAP	£(28,218)	£(29,201)	£(43,868)	£(45,261)	£(37,084)	\$(66,165)
Basic and diluted net loss per share <sup>(4)</sup>	(6.0)p	(5.7)p	(8.3)p	(7.8)p	(6.1)p	\$(0.109)
<b>Principal Reconciling Differences to U.S. GAAP</b>						
Purchase accounting and goodwill	(8,804)	(5,146)	(24,672)	(328)	6,241	11,135
Sale of royalty interest		(2,900)	(7,564)	(19,405)	(12,591)	(22,465)
Revenue recognition		(189)	(1,934)	(26,987)	13,386	23,883
Other reconciling items		(1,276)	(246)	350	(897)	(1,600)

(1) All results, under U.K. GAAP and U.S. GAAP, represent continuing operations.

(2) RTP Pharma Inc. ("RTP") was acquired on December 27, 2001. During the period December 27, 2001 to December 31, 2001 RTP made no contribution to turnover and contributed a loss of £39,000 to the Company's net loss. In the period from July 19, 2001 to December 27, 2001, SkyePharma owned 40.2% of RTP and the results of its operations were included in "Results from associated undertakings". On December 27, 2001



## Edgar Filing: SKYEPHARMA PLC - Form 20-F

SkyePharma achieved control of RTP. RTP was renamed SkyePharma Canada Inc. on April 24, 2002. In 2002, SkyePharma Canada Inc. contributed revenue of £3.9 million, but negatively impacted the full year results by £1.9 million (2001: £0.6 million) primarily due to the amortization of goodwill.

(3)

Administrative expenses in 2003 include an exceptional charge of £9.5 million. This includes a restructuring charge of £2.7 million relating to costs in connection with staff reductions arising from the reorganization of the Company's research and development operations and other business functions. The exceptional charge also includes a further non-cash charge of £4.0 million in respect of the impairment of intellectual property and tangible fixed assets related to the reorganization. In addition, £1.6 million relates to a write-down in the value of investments. A further £1.2 million of the charge relates to the settlement of a licensing dispute.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

(4)

The Company has calculated net (loss)/profit per share data using the weighted average number of shares issued and outstanding for each period as set out in the table above. Basic and diluted (loss)/profit per ordinary share are set out in the table above. In the years ended December 31, 1999 to 2001 and 2003, there is no difference between basic and diluted (loss)/profit per share since all potential ordinary shares including convertible bonds, warrants and options are anti-dilutive. In 2002 there is a difference between basic and diluted (loss)/profit per share due to the existence of dilutive potential ordinary shares at December 31, 2002. Since the number of dilutive potential ordinary shares at December 31, 2002 is small, basic and diluted (loss)/profit per share are the same when expressed to one decimal place.

For information on acquisitions during the years ended December 31, 2002 and December 31, 2001, see Note 29 of the Notes to the Consolidated Financial Statements.

### SkyePharma PLC

<i>Consolidated Balance Sheet Data</i>	As of December 31,					
	1999	2000	2001	2002	2003	2003
	(in thousands, except number of shares)					
<b>U.K. GAAP</b>						
Fixed assets	£83,591	£112,374	£157,391	£165,421	£161,130	\$287,488
Cash and short term bank deposits	13,674	42,878	26,892	28,061	23,240	41,465
Total assets	106,734	163,825	200,583	231,906	202,305	360,953
Net Assets <sup>(1)</sup>	72,057	68,952	95,145	124,270	86,265	153,914
Share Capital	49,409	54,132	58,402	62,546	63,067	112,524
Number of shares	494,086,980	517,322,768	560,023,339	613,458,067	618,669,940	618,669,940
<b>U.S. GAAP</b>						
Total assets	197,557	290,317	306,121	330,907	303,499	541,503
Net Assets <sup>(1)</sup>	157,362	145,929	142,570	138,530	101,732	181,510

(1)

Net Assets is equivalent to shareholders' funds.

For a reconciliation of the Company's U.K. GAAP shareholders' funds to U.S. GAAP, see Note 32 of the Notes to the Consolidated Financial Statements.

## RISK FACTORS

The Company is exposed to certain risks that arise from the activity of developing and manufacturing drug products.

### *Extensive government regulation may cause increased costs and delays in developing and marketing products*

The Company is subject to extensive government regulation. The U.S. Food and Drug Administration ("FDA"), the European Medicines Agency ("EMA") and other national regulatory authorities require rigorous pre-clinical testing, clinical trials and other approval procedures for human drugs. Numerous regulations also govern the manufacturing, safety, labeling, storage, record keeping, reporting and marketing of human drugs. These requirements vary widely from country to country and the time required to complete pre-clinical testing and clinical trials and to obtain regulatory approvals to sell drugs is uncertain. The process of obtaining these approvals and complying with applicable government regulations is time consuming and expensive. If the FDA or other national regulatory authorities require additional clinical trials, the Company could face increased costs and significant development delays before the Company will be able to sell its products commercially. In addition, changes in regulatory policy or additional regulations adopted during product development could also result in delays or rejections in obtaining market approvals from health authorities.

Most of the products that the Company develops will require a new drug application ("NDA") filing with the FDA before they can be marketed in the United States. Based on current practice, the Company expects that it will take less than two years from the date of filing for the FDA to approve an NDA for a product formulation, although the Company cannot predict the exact time required or the outcome of the approval process with any certainty.

A number of products using the Company's technologies have not yet been approved for marketing by regulators. These product candidates are at various stages of development, ranging from pre-clinical studies to Phase III clinical trials and those that have been filed for approval. The Company cannot be certain that it will obtain further regulatory approvals of any of such products. Potential products will require expensive and lengthy testing and regulatory clearances before they can be sold commercially. Products may not prove safe and effective in clinical trials, meet applicable regulatory standards, or be capable of being made at acceptable cost or successfully commercialized. Even if the FDA and other regulatory authorities approve potential products for marketing, the products still may not achieve broad market acceptance. In addition, pre-clinical or clinical testing may not accurately predict safety or effectiveness in broader human use.

### *Competition and technological change may render the Company's products or technologies uncompetitive or obsolete*

The drug development industry is highly competitive and rapidly evolving, with significant developments expected to continue at a rapid pace. The Company's success will depend on maintaining a competitive position and developing efficient and cost-effective products and technologies. The Company's products will compete with other drugs and methods for delivering drugs. The Company cannot be certain that any of its products will have advantages that will be significant enough to cause medical professionals to use them. New drugs or further development in alternative drug delivery methods may provide greater benefits or may offer comparable performance at lower cost than the Company's methods. The Company cannot be certain that developments by other companies will not render its products or technologies uncompetitive or obsolete.

Many of the Company's competitors have longer operating histories and greater financial, marketing and other resources. Such competitors may prove to be more successful in developing competing technologies, obtaining regulatory approvals and marketing their products than the

Company because of greater financial resources, stronger sales and marketing teams or other factors.

The Company will face a variety of competitors with respect to the products it is developing under its collaborative arrangements with leading pharmaceutical companies. Specifically,

products developed and produced by such collaborative arrangements may compete with products produced internally by one or more of the Company's other collaborative partners;

proprietary and generic products developed and produced by such collaborative arrangements may face competition from generic substitutes produced by other companies; and

generic products developed and produced by the Company may compete against branded products produced by one or more of the Company's collaborative partners.

Due to the Company's reliance on the important financial and technological contributions made by the Company's pharmaceutical company partners, any of these outcomes could adversely affect the Company's business.

***The Company's business may give rise to product liability claims not covered by insurance or indemnification***

The design, development and manufacture of the Company's products involve an inherent risk of product liability claims.

The Company has obtained product liability insurance in respect of the pharmaceutical products the Company is developing in conjunction with the Company's collaborative partners although the Company generally relies on indemnity provisions in its agreements with such partners to protect the Company against the possibility of product liability claims. This product liability insurance also covers liabilities associated with the commercial sale of products marketed by third parties using the Company's technology.

The Company has also obtained clinical trial product liability insurance for current human clinical trials and bio-equivalence studies involving its products under development and the Company intends to obtain insurance for future clinical trials and bio-equivalence studies of additional products under development. The Company cannot be certain, however, that it will be able to obtain or maintain any such insurance.

The Company believes that its product liability insurance, together with the indemnity provisions in its collaborative agreements, is adequate for current operations. However, the coverage limits of the Company's insurance or the indemnity provisions in the Company's collaborative agreements may not be adequate to cover all potential claims. Product liability insurance is expensive and may be difficult to obtain or maintain on commercially reasonable terms. A successful claim against the Company in excess of the Company's insurance coverage or outside the scope of the indemnity given by its collaborative partners could adversely affect the results of operations.

***The Company's revenues may be reduced and costs increased as a result of third-party payor cost containment measures***

The Company's ability to achieve profitability in its businesses depends in part on the extent to which appropriate levels of reimbursement for products and related treatments are obtained from government authorities, private health insurers and other organizations, such as health maintenance organizations. These third-party payors are increasingly challenging the pricing of pharmaceutical products. The trend toward managed healthcare in the United States and the growth of organizations such as health maintenance organizations in the United States could significantly influence the purchase of pharmaceutical products, resulting in lower prices and reduced demand

for the Company's products under development. Such cost containment measures could affect the Company's ability to sell products under development and may adversely affect the Company.

***Healthcare reform proposals may adversely affect the Company's business***

The efforts of governments to contain or reduce the cost of health care will continue to affect the business and financial condition of drug companies. A series of health care reform proposals announced in recent years have created uncertainty that could adversely affect the Company's ability to raise funds and to identify and reach agreements with potential partners. If such proposals are eventually adopted, business could be adversely affected. Furthermore, the Company's ability to commercialize potential products may be adversely affected to the extent that such proposals have an adverse effect on the business, financial condition and profitability of other companies that are current or prospective collaborators for some of such products.

***The Company's results of operations tend to fluctuate***

The Company's operating revenues principally derive from contract development. Contract development revenues include milestone payments and that portion of the Company's research and development expenses that the Company charges to its partners pursuant to collaborative arrangements with these partners. The amount of the Company's contract development revenue in any given period will depend on a number of unpredictable factors, including scientific developments, the ability of the Company to find suitable partners, the timing of the negotiation and conclusion of agreements with such partners, whether and when the Company achieves milestones agreed with its partners, such as the timing of regulatory approvals and the market introduction of new products, and other factors. As a result, the Company's results of operations tend to fluctuate materially on a monthly, semi-annually and yearly basis. The Company believes that its revenues will continue to fluctuate in the near to medium term as a result of the factors described above.

***The Company may not achieve or sustain profitability***

In 2002, SkyePharma reported a full year net profit for the first time. In 2003, SkyePharma reported a full year net loss of £43.2 million. As a result of this loss, the Company's consolidated net assets at December 31, 2003 declined to £86.3 million, compared with £124.3 million at December 31, 2002. The loss in 2003 was caused by the fact that three key new deals that the Company had expected to enter into during 2003 were not concluded in that year, delaying the receipt of contract development revenues. Two of these deals have been concluded in 2004 whilst negotiations on the third continue to proceed. The timing of when the Company may achieve profitability is dependent upon the level of milestone payments and license fees received, the timing of contract development revenues and the amount of discretionary investment the Company chooses to make in furthering its own product portfolio and other factors, including those described below, and therefore the Company cannot assure you that it will be able to achieve or sustain profitability. See "Item 5: Operating and Financial Review and Prospects".

Whether the Company will achieve or sustain profitability will additionally depend, among other things, on whether it will, alone or together with its partners, be able to:

develop products utilizing its technologies, either independently or in collaboration with other pharmaceutical companies;

receive necessary regulatory and marketing approvals;

establish and enhance its manufacturing;

achieve market acceptance for such products;

receive royalties on products that have been approved, marketed or submitted for marketing approval with regulatory authorities in line with the Company's current forecasts; and

maintain sufficient funds to finance its activities.



***The Company is dependent on Geomatrix , DepoFoam and inhalation technologies as to which further successful development is uncertain***

The Company's ability to increase revenues and achieve profitability is largely dependent on its Geomatrix , DepoFoam , and inhalation technologies. Approximately 54% of the Company's revenues for the year ended December 31, 2003 derived from royalties, product sales, contract development and milestone payments relating to its Geomatrix technologies, approximately 20% derived from royalties, product sales, contract development and milestone payments relating to its DepoFoam technologies and approximately 18% derived from royalties, product sales, contract development and milestone payments relating to its inhalation technologies. In order to increase revenues from Geomatrix , DepoFoam , and inhalation technologies, the Company must continue to obtain new development contracts with third parties or develop, license and manufacture new formulations of commercially available drugs. The Company cannot assure you that it will be able to obtain such contracts or successfully develop new formulations internally.

The Company has successfully developed six drug products incorporating four of its eight Geomatrix technologies which are currently on the market. The Company is also currently formulating additional products utilizing other Geomatrix technologies which have not yet been approved. One of these technologies, the Multiple Pulse System, has only been subject to limited in vivo (human) clinical testing. Consequently, the Company cannot be sure that drugs utilizing the Multiple Pulse System will be successfully formulated and approved.

The Company has successfully developed two drug products incorporating DepoFoam technologies. The first, DepoCyt® was approved by the FDA in April 1999 and a second product DepoDur (previously referred to as DepoMorphine ), was approved by the FDA in May 2004.

The Company is developing two advanced inhalation technologies to deliver medicines via a patient's lungs without relying on aerosol inhalers powered by chloro-fluoro-carbon ("CFC")-based propellants. The Company has successfully developed one drug product incorporating its inhalation technologies, the Foradil® Certihaler®, which received an approvable letter from the FDA in October 2003 and was approved by the Swiss Pharmaceutical Regulatory Authority in March 2004 and subsequently in Finland and Austria.

The Company cannot assure you that it will be able to develop successfully future products using the Geomatrix , DepoFoam or inhalation technologies. The development and formulation of oral and injectable controlled release and inhalation products is difficult and time-consuming. Each drug compound is different, and there can be no assurance that a drug delivery system that works with one product will work with another.

Even after a product incorporating the Geomatrix , DepoFoam or inhalation technologies has been successfully formulated and approved, its commercial success is not assured. In order to gain medical and commercial acceptance, a product generally must demonstrate some performance improvements and other benefits over products incorporating the same or similar drug compounds. In some cases, these benefits may be difficult to establish.

***The failure by the Company's collaborative partners to fulfill their obligations to the Company to provide funding, obtain regulatory approvals and conduct marketing activities could adversely affect the Company's business***

The Company's ability to develop and market its present and future products depends in large part on its ability to maintain its existing, and enter into new, collaborations with third parties. If any of the Company's partners becomes insolvent or terminates or otherwise fails to fulfill its obligations with the Company, the Company's business could be adversely affected. In particular, the Company faces the following specific risks with respect to collaborative partners:

*Funding.* The Company has entered into a number of collaborative arrangements with leading pharmaceutical companies for the development and commercialization of products using its technologies. Some of the Company's collaborative partners are, however,

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

development stage companies whose business prospects are uncertain and who face similar risks as the Company. If the Company becomes unable to continue to obtain funding for its development activities through its collaborative arrangements or if its collaborative partners fail to make payments due under the development and commercialization agreements, the Company's business would be adversely affected.

*Regulatory Approvals.* In addition, the Company generally depends upon its collaborative partners to secure the necessary regulatory approvals of new pharmaceutical formulations utilizing its technologies. In these cases, the Company has no control over the timing of the regulatory filings and in which countries they may be filed. Its partners may follow a regulatory strategy that does not maximize the royalty income that the Company will receive from its technologies. In addition, the Company's partners may choose not to file for regulatory approval of a product successfully formulated with the technologies. Even if the Company's partners do file for regulatory approval, they may fail to devote the necessary resources and expertise to secure the approval.

*Marketing.* At present, the Company is not involved in the consumer marketing of new products formulated with its technologies and therefore depends on its collaborative partners for such marketing. The majority of the Company's partners are not obligated to market products incorporating its technologies, even if such products are successfully developed and approved. Although the Company has no reason to believe that its partners will not market a successfully developed and approved product, the Company cannot assure you that this will be the case. The Company's future revenues largely depend on the success of such marketing efforts, which are beyond its control. For example, Paxil CR was approved by the FDA in February 1999 but was not launched by GlaxoSmithKline PLC ("GlaxoSmithKline") until April 2002.

***If the Company is unable to obtain additional funding on favorable terms, it would adversely affect the Company's research and development and ability to commercialize its products***

The Company's largest potential cash obligation in the foreseeable future relates to the Convertible Bonds due 2005 in the amount of £59.4 million. The bonds are convertible at the option of the holder into ordinary shares at a conversion price of 83 pence at any time up to June 19, 2005. Unless previously redeemed or converted, the bonds will be redeemed by the Company at the principal amount on June 19, 2005. The Company is evaluating options in the event that the share price is not in excess of the conversion price of 83 pence prior to this date, including the refinancing of the bonds.

If the Company's currently available funds and internally generated cash flow are not sufficient to satisfy its financing needs, the Company would be required to seek additional funding through other arrangements with corporate collaborators, through bank borrowings, through public or private sales of its securities, including equity securities or the renegotiation of the Convertible Bonds due 2005. Any such collaboration could result in limitations on the Company's ability to control the research, development and commercialization of resulting products, if any, as well as its profits therefrom. In addition, the terms of any future bank borrowings could place restrictions on the Company's ability to take certain actions, and any equity financing could result in dilution to the Company's shareholders. The Company does not currently have any committed sources of additional capital. There can be no assurance that the Company will be able to finance the Convertible Bonds due 2005 or that additional funds will be available on a timely basis, on favorable terms or at all, or that such funds, if raised, would be sufficient to permit the Company to continue to conduct its operations. If adequate funds are not available, the Company may be required to curtail significantly, or discontinue, one or more of its research and development programs.



The Company's ability to meet its future capital requirements will depend on many factors. These include:

the Company's ability to maintain existing collaborative arrangements and to establish and maintain new collaborative arrangements with others;

the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;

complying with regulatory requirements;

competing technological and market developments;

changes in the Company's existing research relationships; and

the effectiveness of product commercialization activities and arrangements.

For more information on the Company's liquidity and capital resources, see "Item 4: Information on the Company Business Operations Collaborative Arrangements" and "Item 5: Operating and Financial Review and Prospects".

***A failure to obtain and maintain patents and proprietary rights may adversely affect the Company's business***

The Company's success, competitive position and amount of royalty income will depend in part on its ability to obtain and maintain patent and trade secret protection, particularly for its drug delivery technologies.

The Company believes that patent and other intellectual property protection of its drug delivery and formulation technologies is important to its business and that its future performance will depend in part on its ability to obtain patents, maintain confidential and trade secret information and to operate without infringing the intellectual property rights of others.

While the Company intends to prosecute patents aggressively, the process of obtaining patents is lengthy and expensive. There can be no assurance that patents will be granted in connection with any of the Company's currently pending or future applications or that they will be valid and of sufficient scope and strength to provide the Company with meaningful legal protection or any commercial advantage. In addition, intellectual property protection may be unavailable or limited in some of the countries in which the Company does business. The laws of some foreign countries do not afford the Company's inventions the same degree of legal protection as the laws of the United States. In addition, patent laws may change over time. The Company cannot predict the effect that any such changes would have on its business and its ability to protect commercially sensitive information. If the Company fails to obtain or maintain sufficient protection for its current and future products and technologies, its ability to successfully commercialize these products and technologies could be adversely affected.

The Company, from time to time, may receive notifications of alleged infringement of patents owned by third parties. The Company may not, in all cases, be able to successfully defend itself in court or resolve such allegations through licensing or settlement. Moreover, whether or not the Company is successful in enforcing its own patents or in defending itself against claims of alleged infringements of patents owned by third parties, doing so is time-consuming and costly and may result in the diversion of management resources.

The Company also relies on trade secrets and other unpatented proprietary information in its product development activities. To the extent that the Company relies on trade secrets and unpatented know-how to maintain its competitive technological position, there can be no assurance that others may not independently develop the same or similar technologies. The Company seeks to protect trade secrets and proprietary knowledge, in some cases through clauses in confidentiality agreements with its employees, consultants, advisors and collaborators. Nevertheless, these agreements may not effectively prevent disclosure of the Company's confidential information and may not provide the Company with an adequate remedy in the event of unauthorized disclosure of

such information. If the Company's employees, scientific consultants or collaborators develop inventions or processes independently that may be applicable to the Company's products under development, disputes may arise about ownership of proprietary rights to those inventions and processes. Such inventions and processes will not necessarily become the Company's property, but may remain the property of those persons or their employers. Protracted and costly litigation could be necessary to enforce and determine the scope of the Company's proprietary rights. Failure to obtain or maintain patent and trade secret protection, for any reason, would adversely affect the Company's business.

The Company has entered into a number of collaborative arrangements with leading pharmaceutical companies for the development and commercialization of products. In connection therewith, the Company shares certain of its proprietary knowledge with such collaborative partners. Although the Company's patents and other proprietary rights are designed to protect the Company from infringement by such collaborative partners, there can be no assurance that the Company's patents or other proprietary rights will prevent its collaborative partners from developing similar or functionally equivalent products. In addition, the Company's arrangements with its collaborative partners frequently contain representations, warranties and other assurances given by the Company regarding the scope of its own intellectual property and the non-infringement by the Company of intellectual property owned by third parties. If the Company were found to be in breach of any of these provisions, its partners could sue the Company for damages, which could have a material adverse effect on the Company's business, results of operations and financial condition.

The Company engages in collaborations, sponsored research agreements and other arrangements with academic researchers and institutions, some of which have received and may receive funding from government agencies. Although the Company seeks to retain ownership of all intellectual property rights pertaining to inventions which may result from such collaborations, there can be no assurance that the governments, the institutions or researchers or other third parties will not have rights to such inventions to the extent permitted under applicable law.

For more information on the Company's patents and proprietary rights, see "Patents and Proprietary Rights".

***The Company may not be able to maintain its exclusive technology rights to DepoFoam from the Research Development Foundation***

The Company's DepoFoam business depends in part on its ability to continue to use technology rights that the Research Development Foundation ("RDF") assigned to a subsidiary of the Company, on an exclusive basis. Under the RDF agreement, RDF has the right to terminate the agreement or to convert the exclusive nature of the rights granted under the agreement into a nonexclusive right if the subsidiary does not satisfy its contractual obligations, including making certain minimum annual payments. RDF may also terminate the agreement if the subsidiary becomes bankrupt, breaches the agreement or contests the patents included in this technology. The termination of the subsidiary's agreement with RDF or its conversion to a nonexclusive agreement would adversely affect the Company's DepoFoam business. In April 2004, the Company entered into an amendment agreement with RDF pursuant to which certain commercial terms of the RDF agreement were re-negotiated. As part of the re-negotiation of these terms, 3.25 million SkyePharma ordinary shares were issued to RDF.

***A failure to comply, or the costs of complying, with environmental, health and safety regulations could adversely affect the Company's business***

The Company's business is also subject to regulation relating to the protection of the environment and health and safety, including those governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials. The Company believes that it is in compliance in all material respects with all such laws, rules, regulations and policies applicable to the Company. However, there can be no assurance that the Company will not

be required to incur significant costs to comply with such environmental and health and safety laws and regulations in the future.

***A failure to manage expansion effectively could adversely affect the Company's business***

Management of the Company's growth, as well as the commencement of commercial manufacturing and marketing of the Company's product candidates, will require continued expansion and improvement of the Company's systems and internal controls and an increase in the Company's manufacturing, marketing and sales operations. Any failure to manage growth effectively and on a timely basis could adversely affect the Company's business.

***Any failure by the Company to fulfill its obligations to its collaborative partners in respect of manufacturing and any failure by the Company to enter into new, or maintain its existing, manufacturing arrangements could adversely affect the Company's business***

The Company has its own manufacturing sites in Lyon, France, Muttenz, Switzerland and San Diego, California. However, for the manufacture of certain of its existing products, and certain of those currently in development, including Foradil® Certihaler® and Propofol IDD-D , it will depend on manufacturing partners. If the Company loses one of its current manufacturing partners or fails to enter into agreements with new manufacturing partners, if it experiences delays in finding such partners or if it is unable to enter into commercially viable arrangements with them, its ability to manufacture its existing products and those in development and to meet its obligations in its existing collaborative arrangements, could be adversely affected.

***A failure by the Company's manufacturing facilities to meet required standards could result in delays in manufacturing and additional costs***

Manufacturing operations take place at the Company's facilities in Lyon, France, Muttenz, Switzerland and San Diego, California. Limited manufacturing activities are conducted in Muttenz.

The Company believes that each facility is substantially in compliance with current good manufacturing practices (cGMP) and the applicable regulatory standards. There can be no assurance, however, that the Company's facilities will be found to meet or, in those instances in which a facility has previously been approved for the manufacture of a particular drug, maintain cGMP or applicable regulatory standards. Failure of the Company's manufacturing facilities to meet or maintain such standards could delay or interfere with the Company's plans to scale-up manufacturing or manufacture commercial quantities of its product candidates.

In those instances in which a manufacturing facility has previously been approved, the Company's facilities will need to pass periodic follow-on inspections. The Company will therefore be required to incur a significant additional expenses in order to ensure that its facilities remain compliant with cGMP and the applicable regulatory standards.

***A failure by the Company's to ensure adequate DepoFoam manufacturing capacity could adversely affect the Company's business***

If the Company fails to ensure adequate manufacturing capacity in respect of its DepoFoam manufacturing operations, its business may be adversely affected. In particular, the Company may be unable to supply DepoCyt® to its marketing partners, Enzon Pharmaceuticals, Inc. ("Enzon") for North America, Mundipharma International Holdings Limited ("Mundipharma") for Europe and Eastern Europe and Pharmsis for Brazil, or DepoDur to its marketing partners, Endo Pharmaceuticals Inc. ("Endo") for North America and Medeus Pharma ("Medeus") for Europe. DepoCyt® is currently marketed in the United States and Europe and the Company anticipates the launch of DepoDur in the United States in 2004. For all other DepoFoam products, the Company will need to expand its current manufacturing operations significantly. The Company will also need to comply with regulations in the United States and foreign countries relating to achieving

the prescribed quality and required levels of production of its DepoFoam products and obtaining marketing approval.

***The Company may not be able to obtain the materials necessary to continue to manufacture its DepoFoam products***

The Company currently relies on a limited number of suppliers for materials used to manufacture its DepoFoam products. Some of these materials are purchased only from one supplier. If the Company cannot obtain the materials it needs from its existing suppliers, the Company may not be able to access alternative sources of supply within a reasonable period of time or at commercially reasonable rates. In addition, regulatory requirements applicable to drugs tend to make the substitution of suppliers costly and time-consuming. The unavailability of adequate commercial quantities, the inability to develop alternative sources, a reduction or interruption in supply or a significant increase in the price of materials could adversely affect the Company's ability to manufacture and market its DepoFoam products.

***The Company's manufacturing process may not be suitable for all of the DepoFoam products the Company desires to commercialize***

To date, SkyePharma Inc. has relied on a particular proprietary method of manufacturing its potential DepoFoam products. The Company cannot be certain that this method will be applicable to all potential products it desires to commercialize. The problems that may arise include:

the Company may not be able to meet manufacturing challenges that arise concerning particular drugs to be incorporated in DepoFoam ;

the Company's manufacturing process may not result in viable yields of DepoFoam products; and

the physical and chemical stability of DepoFoam products may vary.

If the Company decides to pursue alternative manufacturing methods for some or all of its drugs, it cannot be certain that these methods will prove to be commercially practical or that it will have the right to use any alternative methods.

***The Company may expend significant time and resources relating to existing and potential legal proceedings and the eventual outcome of such proceedings may differ materially from management's current estimates and beliefs***

The Company is currently involved in various legal proceedings, including actions claiming alleged violations of antitrust laws and infringement of intellectual property rights. Although the Company cannot predict the outcome of these proceedings with certainty, the Company believes, based on information received, that these actions are without merit and is vigorously contesting these claims. Contesting these claims, however, may involve the expenditure of significant management time and resources of the Company. In addition, we cannot exclude the possibility that, contrary to management's current estimates and beliefs, the eventual outcome of such matters could have a material adverse effect on our financial position, results of operations or liquidity. For further information on pending litigation, see "Item 8: Financial Information Legal Proceedings".

***The Company may not be able to obtain the rights to the drugs it desires to deliver through DepoFoam***

The Company's ability to develop and commercialize its DepoFoam technology will depend on whether it and its partners can access the drugs, including small molecule chemical compounds and macromolecule biologics, that are to be delivered through DepoFoam . At times, the Company intends to rely on its partners' ability to provide this access. The Company cannot be certain, however, that its partners will have appropriate drug candidates for its DepoFoam technology. In addition, the Company or its partners may be alleged or determined to be infringing

on third parties' rights and may be prohibited from using the drug or be found liable for damages. Any restriction on access or liability for damages would adversely affect the Company's growth prospects, financial condition and results of operations.

***The Company may incur substantial costs related to its use of hazardous materials***

The Company's research and development involves the controlled use of hazardous materials, chemicals and various radioactive compounds. Although the Company believes that its safety procedures for handling and disposing of such materials comply with the standards prescribed by the applicable regulations, the Company cannot completely eliminate the risk of accidental contamination or injury from these materials. If such an accident occurs, the Company could be held liable for any damages that result and any such liability could exceed its resources and have a material adverse effect on the Company's business, financial condition or results of operations. The Company may incur substantial cost to comply with environmental regulations.

***If the Company is unable to retain key personnel or attract new personnel, it could have an adverse effect on the Company's business***

The Company relies upon a number of key executives and employees, including Ian Gowrie-Smith, its Chairman (Executive Chairman until June 23, 2004), and Michael Ashton, its Chief Executive Officer. In addition, the Company's future operating results depend in part upon its ability to retain and attract other qualified management, scientific, technical, marketing and support personnel. Competition for such personnel is intense, and there can be no assurance that the Company will be able to continue to attract and retain such personnel. The loss of the services of any of the Company's key executives or employees could materially adversely affect the Company.

***Potential conflicts of interests may arise from related party transactions***

The Company and certain of its principal shareholders or their affiliates and other related parties have engaged in several significant transactions among themselves in the past and may continue to do so from time to time in the future. Certain of these transactions provide for significant payments to certain principal shareholders, directors and executive officers upon achievement of specified milestones or profit hurdles. As a result of these arrangements, conflicts of interest may arise between and among the Company, certain principal shareholders, directors and executive officers because of their independent pecuniary interests.

The Company acquired Jago Holding AG and its subsidiaries ("Jago") in May 1996 from Dr. Jacques Gonella, who was, up until June 6, 2001, a Director of the Company, for a combination of cash and shares. In addition to the initial purchase price, the Company agreed to an earn-out arrangement with Dr. Gonella whereby Dr. Gonella was entitled to receive payments dependent on certain revenues related to Geomatrix technologies. On March 31, 2000, certain amendments were made to the 1996 Acquisition Agreement for Jago and a Settlement Agreement was signed establishing the full and final settlement of the deferred consideration payable to Dr. Gonella. For a description of the earn-out arrangement with Dr. Gonella, see "Item 7: Major Shareholders and Related Party Transactions - Certain Arrangements in Respect of the Jago Acquisition".

The Company acquired Krypton Limited ("Krypton") in a share-for-share exchange in January 1996 from a series of trusts in which Ian Gowrie-Smith, who was then Executive Chairman of the Company, certain former directors and a former employee of the Company had interests. Pursuant to an earn-out arrangement, the Company agreed to pay additional consideration of ordinary shares and warrants contingent on a change of control of the Company at not less than specified share price or on the satisfaction of various conditions and hurdles which lapsed on December 31, 2003. See "Item 7: Major Shareholders and Related Party Transactions - Certain Arrangements in Respect of the Krypton Acquisition".

At June 24, 2004, the Company owned 35.7% of Astralis LTD ("Astralis"). The Company is a party to several agreements concerning the development of Astralis' novel injectable vaccine

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

therapy, for the treatment of all forms of psoriasis, a chronic skin disorder. See "Item 7: Major Shareholders and Related Party Transactions Other Arrangements".

At June 24, 2004, the Company owned 24.4% of Vital Living, Inc. ("Vital Living"). The Company has entered into a contract to develop certain products for Vital Living that incorporate its Geomatrix technology. See "Item 7: Major Shareholders and Related Party Transactions Other Arrangements".

At June 24, 2004, the Company owned 18.2% of Micap PLC ("Micap"). During 2003 the Company investigated the pharmaceutical applications of Micap's micro-encapsulation technology in the areas of oral and topical drug delivery. The Company was paid for its services. The Company has exercised an option granted to it under one of its agreements with Micap to complete a technology access and license agreement with Micap. See "Item 7: Major Shareholders and Related Party Transactions Other Arrangements".

Although the Company anticipates that all future related party transactions and agreements will be on terms no less favorable to the Company than it could obtain in comparable contracts with unaffiliated third parties, there can be no assurance that conflicts of interest will not arise between the Company and the principal shareholders or their affiliates in certain circumstances.

### ***Exchange rate fluctuations may adversely affect the Company's results of operations and financial position***

Approximately 60% of the Company's revenues for the year ended December 31, 2003, were derived from customers located outside the United Kingdom. Since the revenue and expenses of the Company's foreign operations are generally denominated in U.S. dollars, Euros and Swiss francs, exchange rate fluctuations between such currencies and the pound sterling will subject the Company to foreign exchange risk with respect to the reported results of its foreign operations. The Company does not currently hedge against the effect of currency translation on its reported results, but does, where appropriate, seek to hedge its exchange rate risk on particular transactions. Fluctuations between local currencies and pounds sterling may materially adversely affect the Company's financial condition and results of operations. See "Item 5: Operating and Financial Review and Prospects".

The Company's ordinary shares trade on the London Stock Exchange in pounds sterling and the ADSs trade on The Nasdaq National Market in U.S. dollars. The value of the ADSs in U.S. dollars may fluctuate as a result of fluctuations in the U.S. dollar/pound sterling exchange rate.

### ***The market prices of the Company ordinary shares and ADSs may be adversely affected by market volatility***

Companies like SkyePharma have, in recent years, experienced dramatic stock price volatility. The following factors may cause the market price of the Company's ordinary shares or ADSs to fluctuate significantly:

announcements of technological innovations or new products by competitors and others;

the status of submissions to the FDA or its international equivalent;

variations in results of operations, market condition, analysts' estimates and the stock market generally; and

stock market perceptions of the pharmaceutical, biotechnology and/ or drug delivery industries specifically.

***Issuances or sales of a substantial number of the Company's ordinary shares or ADSs could adversely affect their market price***

Issuances or sales of a substantial number of ordinary shares or ADSs could adversely affect the market price of the ordinary shares and ADS. As of June 24, 2004, certain principal shareholders and the directors and officers of the Company, as a group, held 34.6% of the Company's outstanding ordinary shares. Shares may be eligible for future sale subject to the conditions imposed by Rule 144 and Regulation S under the Securities Act of 1933. If one or more principal shareholders were to sell a substantial portion of the Company's ordinary shares or ADSs, the trading price of the Company's ordinary shares or ADSs could be adversely affected.

***Principal shareholders may influence the outcome of shareholder approvals and hinder a change in control that might be in your interest***

As of June 24, 2004, certain principal shareholders and the directors and officers of the Company as a group owned approximately 34.6% of the outstanding ordinary shares. As a result, certain directors, officers and such shareholders may be in a position to exert influence in the election of the Company's directors and officers and other corporate actions that require shareholder approval. This concentration of voting powers may hinder changes or corporate actions that are in the interests of other shareholders.

***The Company's shareholders may not receive a return on their shares other than through the sale of their shares***

Under current U.K. law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be paid. The Company has not paid dividends in the past on its ordinary shares. The Company intends to retain earnings, if any, for use in its business and does not anticipate paying any cash dividends in the foreseeable future. Accordingly, other than through the sale of their shares, the Company's shareholders may not receive a return.

#### Item 4: Information on the Company

##### HISTORY AND DEVELOPMENT

###### Overview

SkyePharma PLC is a public limited company organized under the laws of England and Wales with its registered office at 105 Piccadilly, London W1J 7NJ, telephone number + 44 (0) 20 7491 1777. SkyePharma PLC was formerly named Black & Edgington plc and incorporated on March 10, 1910. It was engaged in the provision of temporary structures for major events. In January 1996, the Board of Directors changed the name of the Company to SkyePharma PLC and the nature of its activities to pharmaceuticals. Today the Company is a specialty pharmaceutical company, using its multiple drug delivery technologies (oral, injectable, inhalation, topical and enhanced solubility) to create a product pipeline for out-licensing to marketing partners.

The Company, as currently operated, was formed substantially from the 1996 acquisition of Jago, the 1999 acquisition of DepoTech Corporation and the 2001 acquisition of RTP Pharma Inc. In addition, the Company has acquired certain technologies as set out below.

###### Corporate Acquisitions

Jago, a Swiss drug delivery company which commenced operations in 1983, was acquired by the Company in May 1996. The total consideration paid by the Company to acquire Jago was approximately £100.8 million in cash (plus a prepayment of \$6.0 million (£3.9 million)) and approximately 30.7 million ordinary shares (valued at 75 pence per share). To finance the Jago acquisition and to provide additional working capital for the Company, the Company issued and sold approximately 187.8 million ordinary shares in a public offering in the United Kingdom in May 1996 at a price of 75 pence per share. In the fundraising associated with the transaction, Dr. Gonella, the vendor, purchased 84,789,463 ordinary shares of the Company at a purchase price of 75 pence per share. The Company agreed to pay additional consideration in respect of the Jago acquisition pursuant to an earn-out arrangement. See "Item 7: Major Shareholders and Related Party Transactions - Certain Arrangements in Respect of the Jago Acquisition". On March 31, 2000 a settlement agreement was signed establishing the full and final settlement of the deferred consideration payable to the vendor of Jago, Dr. Gonella. The settlement comprised 6 million ordinary shares and 24 million Deferred Shares. Following the U.S. launch and first commercial sale of Paxil CR by GlaxoSmithKline in April 2002, 12 million Deferred Shares automatically converted into 12 million ordinary shares. The remaining 12 million Deferred Shares will convert into 12 million ordinary shares on the Company's receipt of a royalty statement stating that reported sales of Paxil CR have exceeded (i) \$1,000 million during any calendar year prior to January 1, 2006 or (ii) \$337 million between January 1, 2006 and May 3, 2006. Through the acquisition of Jago, SkyePharma acquired the Geomatrix range of oral controlled release systems and a new generation of inhalation technologies.

In October 1998, the Company acquired 16% of the common stock of DepoTech Corporation of San Diego for a consideration of £2.9 million. On March 10, 1999, the Company completed the acquisition of the outstanding shares by issuing to the former DepoTech shareholders 28,311,070 SkyePharma ordinary shares in the form of ADSs, valued at £20.0 million, plus the right to receive additional shares if one or both of two conditions occur. The conditions were met in 1999 and 2000, further to which the Company issued, in the form of ADSs, an additional 16,177,849 ordinary shares valued at £9.8 million in 1999 and 12,132,600 ordinary shares valued at £13.3 million in 2000. In connection with the acquisition, the Company agreed that outstanding warrants to purchase DepoTech common stock on the effective date of the merger would become warrants to purchase the Company's ordinary shares. Following the issue of shares on April 25, 2000, the former DepoTech shareholders became entitled to a further 458,144 warrants with a value of £0.2 million. Taking into account these final payments, the total consideration paid to acquire DepoTech was £49.4 million. DepoTech had been developing the DepoFoam technology. The DepoFoam



system is a proprietary, injectable technology that provides controlled drug delivery for an extended period of time, improving bioavailability profiles and clinical outcomes. On April 27, 1999, DepoTech was renamed SkyePharma Inc. SkyePharma Inc. is SkyePharma's center for the development and manufacture of injectable, sustained-release therapeutic products.

On July 19, 2001, the Company acquired an initial 40.2% interest in RTP Pharma Inc. of Montreal, Canada for \$20 million (£14.2 million) in SkyePharma ordinary shares and acquired \$5.0 million (£3.5 million) of preferred shares in RTP for cash. RTP specialized in improving the solubility of drugs using its Insoluble Drug Delivery ("IDD") technology platform. During the 90 days following July 19, 2001, the Company acquired an additional \$10 million (£6.9 million) of preferred shares in RTP in return for the issue of additional SkyePharma ordinary shares. On March 13, 2002, the Company announced the completion of the acquisition of the outstanding voting shares in RTP in return for the issue of SkyePharma ordinary shares to the value of \$20.6 million (£14.2 million). The issued shares were subject to selling restrictions, which, other than in limited circumstances, ranged from a minimum of 12 months to 24 months. On April 24, 2002, RTP was renamed SkyePharma Canada Inc. ("SkyePharma Canada"). On March 12, 2003, the selling restrictions on 17,255,926 shares, issued to Elan as a former shareholder of RTP, were lifted. In April 2003, Elan sold its entire shareholding in SkyePharma. In consideration for the loss of the former RTP shareholders' option rights, the Company agreed to issue as deferred consideration 200,000 ordinary shares for each penny difference between 82 pence and the trading price of ordinary shares on June 30, 2003. Since the SkyePharma share price was below 82 pence on June 30, 2003, the Company issued 3,690,211 SkyePharma ordinary shares to the former RTP shareholders. The total consideration of \$60.7 million (£42.0 million) paid to acquire RTP, including acquisition costs, comprised 53,649,578 ordinary shares and \$5.8million (£4.1 million) cash. During 2003, the Company substantially reduced the staff of SkyePharma Canada and outsourced its activities to other SkyePharma sites.

Krypton, a Gibraltar-based company which holds development rights to certain generic drugs, was acquired by the Company in January 1996. The total consideration paid by the Company to acquire Krypton was £12.0 million, satisfied by the issue of 30 million ordinary shares and warrants to subscribe for an additional 3 million ordinary shares at an effective exercise price of 40 pence per share. The Company agreed to pay additional consideration in respect of the Krypton acquisition on a change in control of the Company or if certain milestones and profit hurdles were met. To date, no payments have been made under the Krypton earn-out arrangements and the milestones and profit hurdles lapsed on December 31, 2003. See "Item 7: Major Shareholders and Related Party Transactions - Certain Arrangements in Respect of the Krypton Acquisition".

In January 1997, the Company acquired a pharmaceutical manufacturing and production facility near Lyon, France by acquiring 100% of the issued and outstanding share capital of Laboratories Novalis Production SAS ("Novalis"), a French company, from Wyeth-Ayerst International Inc., ("Wyeth"), a wholly-owned subsidiary of American Home Products Inc. ("AHP"), for a total consideration, excluding acquisition expenses, of two French francs and the assumption of liabilities in the amount of £891,000 arising out of a loan from Wyeth-Ayerst International, which is also a wholly-owned subsidiary of AHP. After the acquisition, Novalis changed its name to Jago Production SAS and later to SkyePharma Production SAS. See "Item 4: Information about the Company - Business Operations - Manufacturing".

### **Technology Acquisitions**

On July 30, 1999, the Company acquired intellectual property, license agreements, know-how and trademarks related to nano-particulate drug delivery technology for the delivery of poorly soluble drugs from Medac GmbH ("Medac"), a private German pharmaceutical company. As consideration for the acquisition, the Company made an initial cash payment of \$2.5 million and issued 3,067,286 ordinary shares with a market value of \$2.5 million to Medac on the date of signing the agreement. The agreement provided for additional consideration in the form of cash and SkyePharma ordinary shares for a total value of \$5.0 million. On April 17, 2000, a further

\$3.0 million in cash was paid to Medac due to compliance by the vendor with certain terms specified in the agreement. On July 21, 2000, the Company issued a further 1,461,455 shares with a market value of \$2.0 million to Medac as deferred consideration due upon the satisfactory transfer of the nano-particulate technology and know-how to SkyePharma. In addition, future royalties will be paid to Medac on net sales of marketed products using nano-particulate technology.

In October 1999, the Company acquired the tangible assets and intellectual property of Hyal Pharmaceutical Corporation in Canada ("Hyal") from the court appointed receiver and administrator of Hyal, for a total consideration of Cdn\$14.0 million (£5.7 million), plus acquisition expenses of £0.2 million. The consideration was satisfied by the set-off of Cdn\$11.6 million of SkyePharma secured and unsecured debt owed by Hyal including the interest due and Cdn\$2.4 million in cash. In addition, and because Hyal was in receivership at this time, SkyePharma indemnified the receiver to the extent that Cdn\$11.6 million exceeded the amount that SkyePharma ultimately was entitled to receive as a creditor of Hyal. This indemnity was secured by an irrevocable letter of credit open for up to one year in the amount of Cdn\$1.0 million. During 2000, the letter of credit was called to recover the shortfall in the receivership process. As a result, in April 2001, SkyePharma received 8.0 million shares representing seven Hyal shares for every dollar shortfall in the receivership process. In addition the Company acquired the 0.7 million shares issued to Meditech Research Limited ("Meditech"), another creditor of Hyal, for Cdn\$0.1 million in May 2001. As a result the total Company shareholding in Hyal (now renamed Cade Struktur) is 0.9 million shares following a 10 for 1 share consolidation. As at June 2004, this represents approximately 10.1% of Cade Struktur. The shares have been recorded at zero cost. Hyal was a drug delivery company that developed products using its topical drug delivery technologies, based on hyaluronan ("HA"), a natural polymer, which are primarily designed to maintain efficacy and localize delivery of drugs to the skin for the treatment of a variety of skin disorders. Following the sale of all related intellectual property and the reorganization of the company, Cade Struktur is now involved solely in the pursuit of financing and development of infrastructure related projects in the former East Germany.

In December 2000, SkyePharma licensed rights to three further topical drug delivery technologies, Crystalip, DermaStick and the ES-Gel system, from Bioglan AB, a Swedish subsidiary of Bioglan Pharma PLC ("Bioglan"). Under the terms of the agreement SkyePharma paid \$9.0 million in cash and obtained certain exclusive development and commercial rights in relation to new products from the Crystalip and DermaStick technologies and also the right to develop with Bioglan two new products using the ES-Gel system.

In May 2002, SkyePharma acquired the entire drug delivery business of Bioglan AB, for £3.6 million in cash, including acquisition costs and the assumption of £0.4 million of net liabilities. The acquired rights included Bioglan's Biosphere® injectable technology and those rights to DermaStick, Crystalip and ES-Gel topical drug delivery technologies that had remained with Bioglan after the January 2001 development and commercialization licensing agreement with Bioglan. The Company has recently announced a reduction in staff at SkyePharma AB and is in the process of transferring its activities to other SkyePharma sites and plans to have completed this by the end of 2004.

On January 14, 2003, SkyePharma announced a strategic investment in Micap PLC ("Micap"), a private company providing patented micro-encapsulation technology to the food, cosmetic, agrochemical and pharmaceutical industries. Micro-encapsulation technology is a process by which tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. These micro-capsules have a number of benefits such as converting liquids to solids, separating reactive compounds, providing environmental protection and improved ease of handling. The Company subscribed for 2,500,000 Ordinary Shares at a price of 80 pence as part of a fundraising of 3,125,000 Ordinary Shares approved by Micap's shareholders at an Extraordinary General Meeting on January 13, 2003. The remaining 625,000 Ordinary Shares were subscribed for by the Sigma Technology Venture Fund, an existing shareholder. In 2003 Micap undertook an initial public offering and as part of the reorganization of Micap in conjunction with the offering, the Company's shareholding was converted into 5,238,334 ordinary shares, representing approximately

18.2% of the ordinary share capital, and 1,830,000 convertible shares. During 2003, SkyePharma investigated the pharmaceutical applications of Micap's micro-encapsulation technology, in the areas of oral and topical drug delivery. The Company was paid for its services. In March 2004, the Company exercised an option granted to it under one of its agreements with Micap to complete a technology access and license agreement with Micap that allows the Company to use Micap's encapsulation technology in up to ten nominated pharmaceutical products to be selected by SkyePharma.

On April 29, 2004 the Company announced that it had licensed the rights to its dermatology assets, which account for substantially all of its topical drug delivery technologies, for those territories that are not covered by existing licenses, to Trigenesis Therapeutics, Inc. ("Trigenesis"). The rights relate to three marketed drugs, including Solaraze®, rights to six pipeline products, including Hyclinda and Acyclovir, and six proprietary and complementary delivery technologies, including HA-based technologies, Crystalip, Dermastick, ES-Gel, Dissocubes and Solid Lipid Nanoparticles. Under the agreement, Trigenesis is obligated to exploit the dermatology assets covered by the license and to continue the development of those drug candidates that are currently at the pipeline stage. Trigenesis has also assumed the majority of SkyePharma's existing obligations to third parties with respect to the development of these drug candidates. All rights granted by the Company to licensees under existing licenses remain unaffected by the agreement. In addition, the Company has retained the right to use the technologies subject to the license for the development of a number of new chemical entities in the dermatology area and, in certain cases, also for non-dermal applications. Subsequent to the completion of the Trigenesis agreement, Trigenesis announced on May 6, 2004 that it was being acquired by Dr Reddy's Laboratories Limited ("Dr Reddy's"), an Indian pharmaceutical company, which will assume all the obligations of Trigenesis.

## BUSINESS OPERATIONS

### Overview

The Company is a specialty pharmaceutical company, using its multiple drug delivery technologies to create a product pipeline for out-licensing to marketing partners. The Company develops novel therapeutic drugs based on its five technology platforms for delivering drugs to the human body: oral, injectable, inhalation, topical and enhanced solubilization.

The following table shows the Company's turnover, operating (loss)/profit and net (loss)/profit for the three years ended December 31, 2003.

	Year Ended December 31, 2001	Year Ended December 31, 2002	Year Ended December 31, 2003
	(in £ thousands)		
Turnover	46,126	69,573	53,152
Operating (loss)/profit	(5,099)	4,716	(39,519)
Net (loss)/profit	(9,452)	1,109	(43,223)

### Oral

A significant part of the Company's business is developing applications of its Geomatrix technologies. Geomatrix is a range of technologies by which drugs taken orally in tablet form are formulated so as to control the amount, timing and location of the release of the drug in the body. There are currently eight Geomatrix technologies designed to meet a wide range of therapeutic objectives. The technologies are flexible and can be modified to apply to a variety of pharmaceutical products.

The Company collaborates with large pharmaceutical companies to develop Geomatrix formulations of their proprietary products. The Company focuses its research and development

efforts on the reformulation of existing drugs using its technologies rather than the discovery of new chemical compounds. In reformulating an existing drug, the Company seeks to enhance the therapeutic and commercial value of the product by creating an improved outcome formulation that may mitigate certain side effects, reduce dosing or help protect against competition from generic drug products. There are six drugs currently being marketed that use the Company's Geomatrix technologies in the following countries:

Paxil CR is marketed in the United States, Canada and certain other countries,

Xatral® OD is marketed in Europe, Canada and other territories in Africa, Asia and Latin America and is marketed in the United States under the name Uroxatral®,

Cordicant-Uno® is marketed in Germany,

Diclofenac-ratiopharm-uno is marketed in Germany,

Madopar DR® is marketed in Switzerland,

Coruno® is marketed in Belgium and Luxembourg.

The Company is also collaborating with several other pharmaceutical companies to commercialize its Geomatrix technologies, including King Pharmaceuticals Inc., Merck KGaA, GlaxoSmithKline PLC and Critical Therapeutics Inc. There are currently three drug candidates using Geomatrix technologies in human studies.

For further information see "Drug Delivery Platforms Oral" below.

### ***Injectable***

The Company's primary injectable technology is DepoFoam. The Company has combined many drugs with DepoFoam in the laboratory and in the clinic and performed studies on these combinations showing that they often achieve sustained controlled release of the drugs. This feature allows the Company to develop new formulations of drug products aimed at treating different diseases and symptoms and/or allowing for more convenient administration by reducing the number or frequency of injections. The potential products include drugs which have already been shown to be useful or potentially useful in humans, as well as new drugs in development at other pharmaceutical companies, which may potentially benefit from DepoFoam. The Company does not conduct research and development to discover new drugs.

The Company has two approved drug products using its DepoFoam technology. DepoCyt® is currently marketed in North America and Europe. DepoDur (previously referred to as DepoMorphine) was approved in the United States in May 2004. It has been licensed to Endo for North America, Pharmis for Brazil and Medeus for Europe. The Company anticipates the launch of DepoDur in the United States in 2004. The Company is currently working on DepoBupivacaine, a DepoFoam formulation of the local anaesthetic bupivacaine, for the treatment of regional pain. The Company is also evaluating, in conjunction with undisclosed corporate partners, DepoFoam formulations of several additional compounds, including small molecule chemical compounds and macromolecule biologics.

The Company's second sustained-release injectable technology is the Biosphere® drug delivery system. In 2003, the Company announced that the Biosphere® technology had been successfully used in pre-clinical studies to deliver a protein drug human growth hormone over an extended period of time. The product has now successfully completed Phase I trials. In addition to the human growth hormone, the Company is also evaluating Biosphere® formulations of other proteins and peptides.

For further information see "Drug Delivery Platforms Injectable" below.

### ***Inhalation***

The Company is developing advanced technologies to deliver medicines via a patient's lungs without relying on CFC-based propellants, which are considered environmentally harmful. The Company is working with two types of such inhalation systems. The first is a metered dose aerosol inhaler ("MDI") that relies on stable drug formulations with non-CFC propellants, hydro-fluoro-alkanes ("HFAs"), to deliver the required therapy. The other is a dry powder inhaler ("DPI"), marketed as "SkyeHaler," that requires no propellant but instead is breath-actuated to deliver drugs in a fine powder suspension. In its MDI development work, the Company focuses on the formulation of drugs for use in MDIs manufactured by others. In its dry powder inhaler development work, the Company focuses both on the development of the device and associated dry powder formulations.

The Company is currently party to a collaboration with AstraZeneca PLC ("AstraZeneca") to develop the next generation of AstraZeneca's Pulmicort® (budesonide) HFA-MDIs for the European market for which Phase III clinical studies in Europe commenced in June 2003. The Company has developed a DPI device with the compound formoterol with Novartis Pharma AG ("Novartis"), the Foradil® Certihaler®, which received an approvable letter from the FDA in October 2003 and was approved by the Swiss pharmaceutical regulatory authority in March 2004 and subsequently in Finland and Austria. The Company has three further collaborative arrangements to commercialize its inhalation drug delivery technology and has a number of other projects at earlier stages of development or being developed internally.

For further information see "Drug Delivery Platforms Inhalation" below.

### ***Topical***

The Company's topical drug delivery technologies are primarily designed to maintain efficacy and localize delivery of drugs to the skin for the treatment of a variety of skin disorders. The Company's portfolio of topical drug delivery technologies consist of HA-based technologies, Crystalip, DemaStick and the ES-Gel system.

The first approved drug product using the Company's HA-based technology is Solaraze®, a topical gel used to treat actinic keratosis, a pre-cancerous skin condition caused by over-exposure to the sun. Solaraze® is licensed to Quintiles Transnational Corp. ("Quintiles") in the United States and to Shire Pharmaceuticals plc ("Shire") in Europe and Australia. It is currently marketed in the United States and various countries in Europe.

In addition to Solaraze, the Company had been developing Hyclinda, a topical gel to treat acne and various other early stage products under its Crystalip, DermaStick and ES-Gel systems. On April 29, 2004 the Company announced that it had licensed the rights to its dermatology assets, which account for substantially all of its topical drug delivery technologies, for those territories that are not covered by existing licenses, to Trigenesis. The rights relate to three marketed drugs, including Solaraze®, rights to six pipeline products, including Hyclinda and Acyclovir, and six proprietary and complementary delivery technologies, including HA-based technologies, Crystalip, Dermastick, ES-Gel, Dissocubes and Solid Lipid Nanoparticles. Under the agreement, Trigenesis is obligated to exploit the dermatology assets covered by the license and to continue the development of those drug candidates that are currently at the pipeline stage. Trigenesis has also assumed the majority of SkyePharma's existing obligations to third parties with respect to the development of these drug candidates. All rights granted by the Company to licensees under existing licenses remain unaffected by the agreement. In addition, the Company has retained the right to use the technologies subject to the license for the development of a number of new chemical entities in the dermatology area and, in certain cases, also for non-dermal applications.

Subsequent to the completion of the Trigenesis agreement, Trigenesis announced on May 6, 2004 that it was being acquired by Dr Reddy's, an Indian pharmaceutical company, which will assume all the obligations of Trigenesis.

For further information see "Drug Delivery Platforms Topical" below.

### ***Solubilization***

Solubility of drugs is an essential factor for all drug delivery systems, independent of the route of administration. Poor solubility leads to a range of problems including poor bioavailability, increased toxicity, variability of absorption when taken with food and poor efficacy. The Company believes that a large number of existing marketed drugs and newly synthesized compounds have solubility problems.

The Company's solubilization technologies consist of two complementary technologies, the nano-particulate and the IDD technologies. Nano-particulate technology aims to improve a drug's solubility by reducing the size of the particules. It has been demonstrated in laboratory testing that the saturation solubility of many drugs can be improved by reducing particle size below one micron in diameter.

The Company is using its solubilization technology platform to enhance the uptake and safety of water-insoluble drugs across a broad range of therapeutic classes including anesthetics, anti-cancer agents and immune suppressants. It is intended that the solubilization technologies will be used to complement and enhance the Company's other drug delivery systems.

The Company currently has a number of proprietary IDD based products in various stages of clinical development including propofol and fenofibrate. The Company granted an exclusive license to the U.S. and Canadian marketing and distribution rights for Propofol IDD-D to Endo and has disclosed alliances with Baxter Healthcare Corporation ("Baxter"), Schering Plough Corporation, and other undisclosed partners on drugs formulated using IDD technology.

For further information see "Drug Delivery Platforms Solubilization" below.

### **Strategy**

The Company has a dual strategy: to become the world's leading specialty pharmaceutical company powered through excellence in drug delivery, and to utilize this expertise and its multiple delivery technologies to create a product pipeline for out-licensing to marketing partners. In addition, the Company will continually strive to maintain its leadership position in drug delivery. The Company's strategy for achieving these objectives consists of the following elements:

*Selectively Fund a Number of Key Projects to a Later Stage of Development.* The Company's strategy in recent years has been to take certain products to a late stage of development, prior to licensing the products to marketing partners. This has allowed the Company to increase its share of the potential revenue streams from these products. An example of this is DepoDur<sup>®</sup>, a product the Company developed through from early stage development to Phase III clinical trials prior to entering into an out-licensing arrangement with Endo for the North American marketing and distribution rights in December 2002 and with Medeus for Europe in April 2004. DepoDur<sup>®</sup> was approved by the FDA in May 2004.

*Develop Existing and New Collaborative Agreements.* In order to increase the market exposure of its products and to capitalize on its collaborative partners' market position and distribution capabilities, the Company intends to continue to develop its projects with its existing collaborative partners and to seek new partners. The Company's existing collaborative arrangements typically provide for a customer-funded development project and contemplate a licensing arrangement (which may be entered into at the same time as the development project or at a later date) under which, if a project is commercialized by the collaborative partner, the Company receives license fees and royalty payments from product sales. In recent years the Company has focused on undertaking additional value added services, such as assuming responsibility for development and regulatory activities, and retaining manufacturing rights that has allowed it to increase its share of the potential revenue stream from these collaborations.

*Commercialization of the Company's Core Technologies.* The Company currently has a portfolio of eight Geomatrix systems, of which four have been commercialized. The Company is focusing on developing and commercializing the remaining four systems, either in conjunction with its collaborative partners or through its own internal development activities. Similarly, of the Company's two injectable depot technologies, DepoFoam and Biosphere®, only DepoFoam has been commercialized to date. The Company will be seeking to develop and commercialize Biosphere® and its other drug delivery technologies.

*Realize Research and Development Synergies between the Company's Technologies.* The Company believes that additional shareholder value can be created by the realization of research and development synergies between the Company's technologies. For example, the ability of the DepoFoam and Biosphere® technologies to encapsulate a wide spectrum of water-soluble drugs, involving small molecules, proteins and peptides, could expand the scope of the Company's inhalation technologies, particularly in the field of proteins and peptides. Additionally, the Company's solubilization technologies will be used to complement and enhance the Company's other drug delivery systems.

*Broadening the Company's Drug Delivery Technology Base.* The Company's pharmaceutical customers are increasingly requesting a broader range of delivery solutions. The Company is currently well placed with its oral, injectable, inhalation, topical and enhanced solubilization technologies. The Company may seek to acquire additional add-on technologies which are complementary to its existing technologies. Management intends to focus on technologies it believes are capable of commercial realization in the near term and will also seek to acquire or license new drug delivery platforms and enabling technologies where it believes they have significant commercial applicability.

*Seek to Retain Manufacturing Rights on Future Collaborations.* The Company believes that retaining manufacturing rights to its products should enable it to capture greater revenue and generate production economies of scale that may not be available to pharmaceutical companies seeking to apply the Company's technologies to only one or a few products. The Company employs personnel who specialize in manufacturing, to commercial quantities, products utilizing the Company's technologies.

## **Research and Development**

The Company's research and development activities are conducted at SkyePharma AG in Muttenz, Switzerland, SkyePharma Inc. in San Diego, United States, SkyePharma AB in Malmo, Sweden and SkyePharma Canada Inc. in Montreal, Canada. As of December 31, 2003, the Company had 294 employees at these four facilities, the majority of whom were engaged in research and development, including 185 scientists, 59 of whom hold Ph.D.s, masters or medical degrees. During 2003, the Company substantially reduced the staff of SkyePharma Canada Inc and outsourced its activities to other SkyePharma sites. The Company has recently announced the reduction of staff at SkyePharma AB and is in the process of transferring its activities to other SkyePharma sites and plans to have completed this by the end of 2004.

The Company conducts research and development both with respect to its own existing products as well as for third parties. The Company accounts for costs incurred in conducting internal research and development activities as research and development expenses and for costs incurred on development work for third party customers as cost of sales. The Company's self-sponsored research and development costs are expensed as incurred.

The Company records amounts received from third parties under the Company's contract development arrangements within turnover, as contract development income. Contract development income represents amounts invoiced to customers for services rendered under development contracts or for milestone payments in accordance with the contract terms. Such amounts are only treated as revenue when the services have been rendered or the specified milestone has been met. Certain refundable income is treated as deferred income until the Company has no further

obligations to make refunds. The Company generally attempts to break even on its development work for third party customers. Therefore, product development activities do not currently have a significant impact on the Company's operating profit/(loss).

Under the Company's agreements with Paul Capital Royalty Acquisition Fund L.P. ("Paul Capital"), announced in 2001 and 2002, Paul Capital provided \$30 million between 2000 and 2002 to fund the clinical development and regulatory submission of DepoDur by the Company, and an additional \$30 million during 2002 and 2003 to principally fund the clinical development of Propofol IDD-D and HFA-formoterol. These funds are recorded as Other Operating Income.

The aggregate amount that the Company spent on research and development and the aggregate amount that was reimbursed by collaborative partners is shown in the table below.

	<b>Consolidated Year ended December 31,</b>		
	<b>2001</b>	<b>2002</b>	<b>2003</b>
	<b>(in £ thousands)</b>		
<b>Research and Development Expenses</b>			
Client sponsored research and development	7,917	12,649	12,085
Internal sponsored research and development	17,918	29,285	30,520
	<b>25,835</b>	<b>41,934</b>	<b>42,605</b>
<b>Contract Development Income</b>			
Client sponsored research and developments reimbursed by:			
Research and development costs recharged	9,857	7,705	5,456
Milestone payments	28,379	47,736	24,196
	<b>38,236</b>	<b>55,441</b>	<b>29,652</b>
<b>Other Operating Income</b>	<b>6,342</b>	<b>14,219</b>	<b>6,126</b>

The Company's research and development efforts in respect of its drug delivery technologies are by their nature subject to risks and uncertainties. There can be no assurance that the products under development can be successfully formulated using any of its drug delivery technologies. In addition, even if such products can be successfully formulated, there can be no assurance that they will secure regulatory approval for the intended medical indication or that SkyePharma formulations approved by regulatory authorities would be capable of being produced in commercial quantities at reasonable costs and successfully marketed.

The Company's development processes are described below. Specific development steps for a product may vary or be unnecessary dependent on a number of factors including the drug delivery technology used and whether the product incorporates an existing marketed active ingredient.

#### ***Development Process for Brand-Name Pharmaceuticals***

The development of improved pharmaceuticals formulations using one of the Company's drug delivery technologies takes place in several steps. The first step, called the "preliminary assessment", is to assess the suitability of the drug candidate for a particular drug delivery system through various techniques including the use of sophisticated computer modeling. During the preliminary assessment, the Company will analyze product specifications provided by the client. If the preliminary assessment indicates that the drug candidate is suitable for formulation with the drug delivery technology, the project will proceed to development as follows:

*Feasibility.* At this stage, the Company conducts an in vitro (laboratory) feasibility study to determine whether, under laboratory conditions, the formulation of the product candidate can be achieved. The Company may develop up to 20



prototype formulations for in vitro feasibility studies and selects the most promising two or three for further study and analysis.

*Pilot Trials.* Once a successful feasibility study has been conducted, small batches of the selected prototypes are manufactured by the Company or its collaborative partners for in vivo (human) testing in pilot trials. Pilot trials involve at least 12 healthy volunteers. The purpose is to determine whether the in vitro results can be replicated in humans. Pilot trials are generally managed by the Company and conducted by a third party clinical research organization ("CRO"). If the pilot trials demonstrate sub-optimal results, the product candidate may be reformulated and new pilot trials conducted.

*Scale-up/Bio-Batch.* After a successful pilot trial, the Company or its collaborative partners will manufacture a commercial scale batch or a "bio-batch" (at least one tenth of the projected commercial batch size). The purpose of this stage is to develop and validate the process by which the product will be manufactured. If formulation changes are made during scale-up/ biobatch, additional in vivo testing may be performed in pre-pivotal trials involving a small patient population.

The "pre-clinical" phase of development referred to in parts of this document means additional testing following initial feasibility studies and other studies, including additional animal studies, necessary to prepare and file an Investigational New Drug ("IND") application. For a more comprehensive description of the requirements of an IND, see "Government Regulation United States NDA Process" below.

*Phase I Trials.* The first stage in the clinical development plan is to conduct Phase I clinical trials. These studies are usually performed to generate preliminary information on the chemical action of the compound, the activity or fate of the product in the human body over a period of time including adsorption, distribution, metabolism and elimination ("ADME"), and safety of the drug using normal healthy volunteers and patients. Phase I trials involve approximately 12-30 healthy volunteers. These trials are generally managed by the Company and conducted by a CRO that has a Phase I clinical study unit.

*Phase II Trials.* The second stage in the clinical development plan is to conduct Phase II clinical trials. These trials are generally carried out on patients with the disease or condition for which the new pharmaceutical formulation is being developed. The main purpose is: to provide preliminary information on the positive effects of the treatment and whether the effects are correlated with the administered doses in one or more demographic groups, assess various measures of patient benefit for use in Phase III trials, and to supplement safety information obtained from Phase I trials. The Company, in collaboration with its partner, or the partner, manages the trial activities (from protocol development through to the writing of the study final reports). The Company may use a CRO to complete the trials. Phase II studies may not be required for improved pharmaceutical formulations of an existing drug if it is targeted at the same indication as the existing drug.

*Pivotal (Phase III) Trials.* The last step of the development process is a number of pivotal (Phase III) trial of the product formulation in an expanded patient population to support the approval of marketing applications. Typically, the studies will be performed in the United States, Canada and Europe to facilitate a multi-national product registration process. In addition, drug companies typically conduct separate clinical trials for Japan for drugs intended to be marketed in that country. Either the Company, in collaboration with its partner, or the partner manages the trial activities (from protocol development until the writing of the final study reports). The Company may use a CRO to complete the studies on schedule.

*Regulatory Filing.* The Company, in collaboration with its partner, or the partner manages all regulatory activities during the product development phases until product approval. These activities include submissions, communication and meetings with health authorities and the preparation of marketing approval applications.

## Drug Delivery Platforms

This section provides a more detailed description of the Company's various drug delivery platforms and their application to particular drugs and drug candidates.

### *Oral*

#### *The Geomatrix Oral Technologies*

The original Geomatrix technology was developed by a team of researchers at the University of Pavia in Italy in the early 1980s. Subsequently, the Company acquired the technology and pursued the development of the Geomatrix platform of oral controlled-release systems. The effort has produced a platform of proprietary Geomatrix controlled-release systems that can be applied to a broad range of drugs on a commercial scale.

The Geomatrix systems control the amount, timing and location of the release of drug compounds in the human body. Geomatrix technologies can improve the efficacy of orally administered drugs and enhance compliance by patients with prescribed medical treatments by permitting the drug to be taken less frequently, by reducing side effects and by causing the drug to be released at more specific locations within the body. This is achieved through the construction of a tablet with two basic components: a core containing the active drug or drugs in an hydrophilic methylcellulose, or "HPMC", matrix formulation and one or two additional barrier layers. The HPMC matrices govern the release profile of a drug dependent on the viscosity of the HPMC used whilst the barrier layers control the surface area diffusion of the drug or drugs out of the core. The "release profile" refers to the rates at which a drug tablet releases the active drug component over the period of time after the drug is taken. In addition, the tablet may be coated if, for example, this would ease any gastric irritation that otherwise would be caused by the drug compound, or for other functional purposes.

The combination of different chemical components in the core and barrier layers, each with different rates of swelling, gelling and erosion, allows the production of tablets with a wide range of predictable and reproducible drug release profiles. The rate of drug release is a function of the viscosity of the HPMC and the exposed surface area from which the drug diffuses. When the tablet is first swallowed, the drug concentration is high but the surface area is small; as time goes by and the core swells, the surface area expands to compensate for the decrease in drug concentration.

The Company believes that the Geomatrix systems enjoy a competitive advantage in the drug delivery industry because of the ease with which Geomatrix tablets can be manufactured. Unlike certain competing drug delivery systems that require off-site, customized production equipment and methods, Geomatrix tablets can be manufactured by readily available equipment that can be incorporated into widely used pharmaceutical production processes. In this way, Geomatrix may afford the pharmaceutical partner direct control over its production strategy while other drug delivery systems may entail incremental risks or costs related to their off-site, customized production requirements.

In addition to ease of manufacturing, the Company believes that the key features of the Geomatrix technologies are as follows:

**Custom Design.** Geomatrix formulations of drugs can be designed to deliver the release profile required by the client pharmaceutical company and drugs can be combined with other active substances to improve their effectiveness.

**Versatility.** Geomatrix can be applied to a wide range of small molecule drugs, including some with poor water solubility, and can target the site of release.

**Controlled Rate of Diffusion.** Geomatrix formulations can control the rate of drug diffusion throughout the release process, ensuring 100% release of the active drug.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

**Reproducibility.** Use of conventional high speed tableting processes allows a high degree of product consistency and uniformity.

**Complete Disintegration.** Geomatrix tablets disintegrate completely in the patient's digestive system and leave no solid residue.

**Release Profiles.** The flexibility of the Geomatrix technologies has enabled the Company to create a number of release profiles suitable for a broad variety of pharmaceuticals.

The following sets forth a brief description of the Geomatrix systems.

**Zero Order Release.** The Zero Order Release system provides a constant rate of drug release over a defined period of time. It is used primarily for drugs with short half-lives so that constant blood levels of the active drug compounds can be maintained with fewer doses. The Company has three approved Zero Order Release formulations currently on the market: Cordicant-Uno® in Germany, Coruno® in Belgium and Luxembourg and Xatral® OD/Uroxatral® in United States, Canada, Europe and other territories in Africa, Asia and Latin America. Paxil CR, currently marketed in the United States, Canada and certain other countries, has been developed using a combination of the Zero Order and Positioned Release technologies.

**Binary Release.** The Binary Release system is used to provide the controlled-release of two different drugs in a single formulation. The drugs may be released at different rates and times, if desired. This system is designed for drugs that work best in combination. The Company has one Binary Release formulation currently on the market: Madopar DR® in Switzerland.

**Quick Slow Release.** The Quick Slow Release system provides a quick burst of drug release followed by a constant rate of release over a defined period of time. It is used primarily in drugs, such as arthritis medications, in which it is desirable to have an initial burst of release to achieve maximum relief in a short amount of time followed by a constant rate of release for sustained therapy. The Company has one approved Quick Slow Release formulation currently on the market: Diclofenac-ratiopharm-uno in Germany.

**Slow Quick Release.** The Slow Quick Release system provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time. This release profile is designed for medications to treat diseases, such as angina, that would benefit from increased therapy when the patient is sleeping because of the high incidence of nocturnal attacks.

**Positioned Release.** The Positioned Release system is designed to deliver the tablet to a predetermined position in the digestive system before it begins to release the active drug compounds. This system is best suited to drugs for which it is desirable to begin release at a certain point in the gastrointestinal tract, for example in the case of drug compounds that are best absorbed by the human body at particular points in the upper gastrointestinal tract. Paxil CR, currently marketed in the United States, Canada and certain other countries has been developed using a combination of the Zero Order and Positioned Release technologies.

**Accelerated Release.** The Accelerated Release system provides a constantly accelerating rate of drug release. This system is well suited for drugs such as H<sub>2</sub>-receptor antagonists that are preferentially absorbed in the upper part of the gastrointestinal tract.

**Delayed Release.** The Delayed Release system provides a predetermined time lag before it begins releasing drug molecules. This system is designed for drugs such as certain cardiovascular medications for which the desired dosing time may be several hours after the patient takes the drug.

**Multiple Pulse.** The Multiple Pulse system provides an initial quick burst of drug release followed by a predetermined period of no release followed by a second burst of drug release. This system is designed for treating diseases that require suppression or activation



## Edgar Filing: SKYEPHARMA PLC - Form 20-F

of a specific receptor twice a day where the receptor needs to be reset between drug interaction, such as appetite suppression and Attention Deficit Disorder. To date, the Multiple Pulse system has only been subject to limited in vivo (human) clinical testing.

Products formulated with the Zero Order, Binary Release, Quick Slow and Positioned Release systems are currently on the market. There can be no assurance, however, that the Company will be able to develop successfully future products incorporating such delivery systems. At present, there are no products on the market that have been formulated with the Company's Slow Quick, Accelerated Release, Delayed Release or Multiple Pulse systems. The Company is actively developing formulations utilizing some of these and other drug delivery systems, but there can be no assurance that these efforts will be successful.

### *Approved Geomatrix Products*

To date, seven Geomatrix formulations of pharmaceutical products have received regulatory approval. Six of these products are currently marketed, one in the United States, Europe, Canada and other territories in Africa, Asia and Latin America (Xatral OD/Uroxatral®), one in the United States, Canada and certain other countries (Paxil CR), two in Germany (Cordicant-Uno® and Diclofenac-ratiopharm-uno), one in Switzerland (Madopar DR®) and one in Belgium and Luxembourg (Coruno®).

The following table sets forth certain information regarding the approved Geomatrix products:

Product	Indication	Regulatory Approvals and Year of First Approval	Geomatrix System	Collaborative Partner
Paxil CR	Depression	United States (1999)	Positioned Release/Zero Order	GlaxoSmithKline
Xatral® OD/Uroxatral®	Genito-Urinary	United States (2003) Europe (2000)	Zero Order	Sanofi-Synthélabo
Madopar DR®	Parkinson's Disease	Switzerland (1996)	Binary	Hoffmann-La Roche
Coruno®	Angina	Belgium (2002) Luxembourg (2003)	Zero Order	Therabel
Cordicant-Uno®	Hypertension	Germany (1994)	Zero Order	Mundipharma
Diclofenac-ratiopharm-uno	Arthritis	Germany (1995)	Quick Slow	ratiopharm
Dilacor® XR	Hypertension and Chronic Stable Angina	U.S. (1992)	Zero Order	Watson

*Paxil CR* is a modified release version of Paxil/Seroxat (paroxetine HCL) using a combination of the Positioned Release and Zero Order Geomatrix systems. Paxil is an FDA-approved drug that is currently marketed primarily in the United States and Europe and is an immediate release formulation prescribed for central nervous system disorders. According to information published by GlaxoSmithKline on its website, Paxil had worldwide sales in 2003 of £1.9 billion of which £1.2 billion was in the United States.

*Paxil CR* was filed with the FDA by SmithKline Beecham (now part of GlaxoSmithKline) in December 1997 and approved by the FDA in February 1999 for the 12.5 and 25mg dosage forms. In early 2001, GlaxoSmithKline, the Company's collaborative partner in the development of Paxil CR, announced that it had received an approvable letter from the FDA for a second CR indication, panic disorder. On April 19, 2002, Paxil CR was launched in the United States for the treatment of central nervous system and panic disorders.

In September 2003, GlaxoSmithKline announced that the FDA had approved an additional therapeutic application for Paxil CR in the continuous treatment of premenstrual dysphoric disorder ("PMDD"). In October 2003, GlaxoSmithKline further announced that the FDA had

approved Paxil CR for the treatment of social anxiety disorder, making Paxil CR the only controlled-release selective serotonin reuptake inhibitor antidepressant approved for this indication. In January 2004, the Therapeutic Products Directorate of Health Canada approved Paxil CR for the treatment of central nervous system disorders, panic disorder and social anxiety disorder. In February 2004, GlaxoSmithKline announced that the FDA had approved Paxil CR for a fifth therapeutic application for the intermittent treatment of PMDD.

*Xatral® OD* is a once daily Zero Order Geomatrix formulation of alfuzosin used for the treatment of the functional symptoms of benign prostatic hyperplasia, a common condition in men over the age of 50, that was developed in conjunction with Sanofi-Synthélabo. Xatral is available in more than 80 countries world-wide as a two or three times a day formulation.

In January 2000, Sanofi-Synthélabo announced that it had received the first batch of European marketing approvals for Xatral® OD. In December 2000, Sanofi-Synthélabo submitted an NDA with the FDA for Xatral® OD. In October 2001, Sanofi-Synthélabo announced that an approvable letter had been received from the FDA for Xatral® OD, registered in the United States as Uroxatral®. Additional data requested by the FDA was filed by Sanofi-Synthélabo in December 2002. On June 16, 2003, the Company announced that the FDA had approved Sanofi-Synthélabo's NDA for Xatral® OD, to be marketed in the United States as Uroxatral®. Uroxatral® was launched in the United States in November 2003 and in March 2004 Sanofi-Synthélabo announced that it had begun to market Uroxatral® directly to primary care physicians in the United States. In addition to the United States the product is now launched throughout Europe, Canada and other territories in Africa, Asia and Latin America. Sanofi-Synthélabo is currently developing Xatral® OD for a second indication, acute urinary retention, which was approved in certain countries in Europe in 2004 and filing is anticipated by Sanofi-Synthélabo in the United States in 2005.

*Madopar DR®* is a once per day Binary Geomatrix formulation of levodopa and benzerazide, a combination therapy indicated for the treatment of Parkinson's Disease, which is approved for sale in Switzerland. Madopar DR® was developed in conjunction with Hoffmann-La Roche AG (part of Roche). The Binary Geomatrix formulation of levodopa and benzerazide optimizes patient therapy and convenience by providing for the release of an enzyme inhibitor along with the drug compound without the co-administration of two pills. The Company is manufacturing this product for the Swiss market on behalf of Roche at its facility in Muttenz, Switzerland.

*Coruno®* is a once per day Zero Order Geomatrix formulation of molsidomine, currently marketed in Europe and used to treat angina pectoris, a common symptom of coronary heart disease. Coruno® was developed in conjunction with the Therabel Group ("Therabel") and was approved by the Belgian regulatory authorities in 2002 for marketing in Belgium. Coruno® was launched by Therabel in April 2003. Subsequently, Coruno® was approved and launched in Luxembourg. The Geomatrix controlled release technology in Coruno® enhances patient compliance and convenience by reducing the dosing requirement to once per day.

*Cordicant-Uno®* is a once per day Zero Order Geomatrix formulation of nifedipine, a calcium channel-blocking agent indicated for hypertension, which is approved for sale in Germany. Cordicant-Uno® was developed in conjunction with and is marketed by Mundipharma, a private German pharmaceutical company. The Geomatrix controlled release technology in Cordicant-Uno® enhances patient compliance and convenience by reducing the dosing requirement to once per day. The Company does not currently receive any revenues from this product.

*Diclofenac-ratiopharm-uno* is a once per day Quick Slow Geomatrix formulation of diclofenac, a nonsteroidal anti-inflammatory drug indicated for the acute and chronic treatment of rheumatoid and osteo-arthritis. Diclofenac-ratiopharm-uno, which is approved for sale in Germany, was developed in conjunction with and is marketed by ratiopharm, a private German pharmaceutical company. The Geomatrix controlled-release technology in Diclofenac-ratiopharm-uno optimizes patient therapy by providing an initial burst of the drug for quick relief followed by a controlled-release for sustained therapy. It also optimizes patient compliance and convenience by reducing the dosing requirement to once per day.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

*Dilacor® XR* is a once per day Zero Order Geomatrix formulation of diltiazem hydrochloride, a calcium channel-blocking agent indicated for hypertension and for the management of chronic stable angina. Dilacor® XR was developed in conjunction with Rhône Poulenc Rorer (now part of Aventis Pharma). In June 1997, Rhône Poulenc Rorer granted Watson Pharmaceuticals an exclusive worldwide license to market Dilacor® XR. In addition to being approved in the United States, Dilacor® XR is also approved for sale in Australia, New Zealand, Korea, the Philippines and Germany. Marketing exclusivity for this product in the United States expired in June 1995. The Company no longer receives royalties from this product.

### *Geomatrix Products in Development*

There are currently five products in the development process that utilize the Geomatrix technologies. In addition, the Company has a number of projects in earlier stages of development. The following table sets forth certain information regarding some of the products in the Company's development pipeline. For a description of the development process, including definitions for development status stages, see "Research and Development Development Process for Brand-Name Pharmaceuticals".

Product	Modified	Therapeutic Category	Development Status	Collaborative Partner
Ropinirole	Yes	Central Nervous System	Phase III	GlaxoSmithKline
Zileuton	Yes	Asthma/COPD	Phase II completed	Critical Therapeutics
Undisclosed #1	Yes	Undisclosed	Phase II completed	Merck KGaA
Ramipril	Yes	Cardiovascular	Feasibility	King
Undisclosed #2	Yes	Undisclosed	Feasibility	Undisclosed

*Ropinirole* is an FDA-approved drug that is currently marketed as Requip®, primarily in the United States and Europe, by GlaxoSmithKline. As it is currently marketed, Requip® is an immediate release formulation administered three times daily and is prescribed for Parkinson's disease, a chronic progressive disease in which the degeneration of nerve cells in the brain eventually impairs the ability to control body movements. The Company is currently developing a once-daily version using its Geomatrix technology. The Geomatrix formulation is expected to provide a simplified regime for patients on Requip® therapy that will improve patient convenience. The once-daily version commenced Phase III clinical trials in June 2003.

*Zileuton* is an FDA-approved drug for asthma and COPD. A four times a day immediate-release version of zileuton was marketed by Abbott Laboratories as Zyflo® Filmstab® (zileuton tablets). SkyePharma has developed a controlled-release formulation of Zileuton, using its Geomatrix technology. Abbott completed Phase III development in asthma with this product. In January 2004 SkyePharma announced an agreement with Critical Therapeutics Inc ("CTI") to collaborate on the further development of this formulation for the indications of moderate to severe asthma and COPD. Because of changes in the active pharmaceutical ingredient supplier and manufacturer, the formulation will need further in vivo (human) testing before an application may be filed. Once approved by the FDA, CTI intends to market this product in the United States through its own specialist sales force.

*Undisclosed # 1* is a new formulation of a drug being developed for Merck KGaA ("Merck") utilizing the Geomatrix delayed release technology to deliver the dose at a precise time interval after administration. The new formulation being developed by the Company has completed Phase II development. The Company is in discussion with Merck regarding the future development of this product.

*Ramipril* is an FDA-approved drug that is currently marketed in the United States and Puerto Rico as Altace® by King Pharmaceuticals, Inc. for the treatment of hypertension and post heart



attack congestive heart failure. The Company is developing a modified-release formulation which should provide the product with extended duration of action and improved bioavailability. The new formulation being developed by the Company is in the feasibility stage.

*Undisclosed # 2* is a new formulation of a drug being developed for an undisclosed partner utilizing the Geomatrix technology to control the release of the drug from the tablet and at the same time increase the drug's bioavailability. The new formulation being developed by the Company is in the feasibility stage.

#### *Other Oral Products in Development*

*NK-104* is a new lipid-lowering agent that has been developed by Kowa and has received marketing authorization in Japan. Phase II trials have been completed in Europe and have commenced in the United States. NK-104 has been developed from a class of compounds called statins that have been shown to significantly reduce mortality in patients with high cholesterol and heart disease. The Company and Kowa have an active relationship involving the formulation, development, scale-up and manufacturing for clinical trials for a number of products in Kowa's development pipeline, including NK-104.

#### *Injectable*

##### *DepoFoam Injectable Technologies*

DepoFoam consists of lipid-based particles composed of hundreds to thousands of discrete water-filled chambers, containing the encapsulated drug, with each chamber separated from adjacent chambers by a lipid membrane. The particles are suspended in saline and the water-filled chambers containing the active ingredient. DepoFoam formulations can be delivered into the body by a number of routes, including under the skin, within muscle tissue, into brain and spinal fluid, within eyes, within joints and within the abdominal cavity. Because the components of DepoFoam are similar to lipids normally present in the body, the material is biodegradable and biocompatible. Typically, a DepoFoam formulation consists of less than 10% lipid to encapsulate the active drug to form DepoFoam particles that are suspended in solution (generally saline) that accounts for approximately 90% of the remaining volume. The resulting DepoFoam formulation is stored under refrigeration in ready-to-use form.

SkyePharma Inc. has tested DepoFoam formulations that release drugs over a period of days to weeks with the period of release defined by characteristics of a variety of DepoFoam formulations and the relevant drug. SkyePharma Inc. believes drugs may be released from DepoFoam particles as the drugs diffuse through the walls, by gradual erosion of the particles, and by processes involving the rearrangement of membranes. The nature of drug release may also be determined by the characteristics of each drug molecule. SkyePharma Inc. has demonstrated that DepoFoam can be used to encapsulate a wide spectrum of drugs, including small molecules, proteins, peptides, antisense oligonucleotides and DNA, aimed at treating different diseases and symptoms.

##### *Advantages of DepoFoam*

The Company believes DepoFoam addresses many of the limitations associated with traditional methods of delivering drugs. Most drugs are administered orally, by injection in intermittent and frequent doses or by continuous infusion. These latter methods of administration are not ideal for several reasons, including difficulty in achieving appropriate drug levels over time, problems with side effects, high costs due to frequent or continuous administration and poor patient compliance. Furthermore, innovations in biotechnology have led to an increase in the number of macromolecule biologics, such as protein and peptide drugs, under development. These drugs, because of their large molecular size and susceptibility to degradation in the gastrointestinal tract or in the blood, must usually be administered by multiple injections, often in a hospital or other clinical setting.

The Company believes that DepoFoam's key advantage over traditional methods of drug delivery, including injections and oral administration, is that the sustained-release characteristics of DepoFoam allow drugs to be administered less frequently and more conveniently. To attain the desired effect, conventional drug delivery often results in a dosage that delivers an initially high level of the drug followed by a sharp decline over a relatively short period of time, whereas DepoFoam formulations can provide a more consistent drug level over an extended period. As a result, DepoFoam products can potentially improve safety and effectiveness. For example, DepoCyt® clinical trials have shown that DepoCyt® has a therapeutic life of up to two weeks after a single intrathecal injection compared with less than one day with unencapsulated cytarabine.

The Company believes that key features of DepoFoam, including lower initial drug levels and delivery of appropriate drug levels over an extended period of time, make it superior not only to traditional methods of delivering drugs, but also to other sustained-release delivery formulations. The Company believes DepoFoam may:

*Enhance safety and efficacy.* DepoFoam drug delivery may improve the ratio of therapeutic effect to side effects by decreasing the initial concentrations of drug associated with side effects, while maintaining levels of drug at therapeutic, sub-toxic concentrations for an extended period of time.

*Improve convenience and lower overall treatment costs.* DepoFoam formulations of drugs may offer cost savings by reducing the need for continuous infusion, the frequency of administration and the number of visits a patient must make to the doctor.

*Expand types of drugs which can be delivered over an extended period of time.* DepoFoam may be able to deliver proteins, peptides and nucleic acids more effectively.

*Expand indications of currently marketed drugs.* The appropriate release of drugs from a DepoFoam formulation may allow such drugs to be marketed for indications where they are currently not thought to be useful because of the limitations of current delivery methods.

*Improve products through reformulation.* DepoFoam may offer the potential to produce new formulations of generic products that may be differentiated from the nonsustained-release versions by virtue of reduced dosing requirements, improved effectiveness, additional applications or decreased side effects.

#### Approved DepoFoam Injectable Products

To date, two products utilizing the Company's DepoFoam Injectable technology have received regulatory approval. Of these products, DepoCyt® is currently marketed in the U.S. and Europe. DepoDur was approved by the FDA in May 2004 and the Company anticipates its launch in the United States at the end of 2004. DepoDur is currently under review by regulatory authorities in Europe.

<b>Product</b>	<b>Indication</b>	<b>Regulatory Approvals and Year of First Approval</b>	<b>Marketing Partner</b>
DepoCyt®	Oncology	United States (1999) Europe (2001)	Enzon Mundipharma
DepoDur DepoCyt®	Post-operative pain	United States (2004)	Endo

DepoCyt® combines the Company's DepoFoam technology with cytarabine, a drug used to treat neoplastic meningitis from lymphomas and solid tumors. It is currently marketed in North America by Enzon and in Europe and Eastern Europe by Mundipharma for the treatment of lymphomatous meningitis. It is licensed for distribution to Nippon-Shinyaku in Japan and to Pharmis Biofarmaceutica for Brazil.



*Background*

Cancer from solid tumors, leukemia (a form of cancer involving white blood cells) or lymphomas (a form of cancer involving tissues of the lymphatic system) can spread to the soft tissue membrane of the brain and spinal cord. This type of cancer is called neoplastic meningitis. Because of the blood-brain barrier, drugs in the bloodstream do not penetrate well into the fluid which surrounds the brain and spinal cord. Thus, when cancer cells spread to this membrane, the most effective therapy is to inject anti-cancer drugs directly into the fluid which surrounds the brain and spinal cord. Cytarabine is one of several drugs most commonly used for this therapy. Cytarabine acts by inhibiting a vital enzyme in DNA synthesis, resulting in death of a dividing cell. Therefore, the best results are obtained when the drug is localized in the vicinity of dividing cancer cells for an extended period.

Cytarabine does not last long in the fluid surrounding the brain and spinal cord. The result is that neoplastic meningitis cannot be treated effectively without the use of repeated injections into the space between the brain and/or spinal cord and the membrane which surrounds them. These injections are inconvenient and uncomfortable for patients, require physician supervision and increase the risk of infection. Because of these and other factors, the disease is often under-diagnosed and frequently left untreated. Without effective treatment, life expectancy for patients diagnosed with this disease is between two and four months. Clinical trials to date have shown that DepoCyt® maintained concentrations of cytarabine in the fluid which surrounds the brain and spinal cord for up to two weeks after a single injection as compared to less than one day with traditional injections of cytarabine. As a consequence, the use of DepoCyt® results in less frequent injections and may extend effective levels of the drug in the space between the brain and/or spinal cord and the membrane which surrounds them.

*Clinical Development*

DepoCyt® was developed in collaboration with Chiron Corporation in the United States and, until June 2000, with Pharmacia & Upjohn S. p. A., an affiliate of Pharmacia Corporation. Since April 1994, SkyePharma Inc. has been conducting clinical trials of DepoCyt® for the treatment of these cancers.

In April 1999, the FDA approved DepoCyt® for the treatment of neoplastic meningitis from lymphomas and the product was launched in the United States in May 1999. In October 1999, SkyePharma Inc. discovered that two lots of DepoCyt® did not meet specifications and recalled these lots. Investigations identified that unannounced changes in a supplier's manufacturing process for a raw material resulted in product which did not meet all specifications throughout the shelf-life. SkyePharma Inc. and Chiron Corporation voluntarily withdrew DepoCyt® from the market. There were no adverse events attributed to the recalled batches, and the product was made available to patients on a compassionate basis. In March 2001, the FDA gave clearance to return DepoCyt® to the market.

In November 1999, SkyePharma Inc. received marketing approval for DepoCyt® from the Canadian regulatory authorities for the treatment of neoplastic meningitis from lymphomas and solid tumors. The Canadian marketing and distribution rights were licensed to Paladin Labs Inc. in June 2000.

Pharmacia Corporation filed for marketing approval of DepoCyt® to be used in the treatment of cancers which have spread to the brain and spinal cord from both the lymphatic system and solid tumors in Europe. In October 1999, its filing was accepted by the regulatory authority. In June 2000, Pharmacia Corporation notified the Company that it was terminating the marketing and distribution agreement with the Company for DepoCyt®. Pharmacia Corporation assigned the European marketing application to the Company, and the Company continued to pursue European marketing approval.

In April 2001, the Company received notification that the European Committee on Proprietary Medicinal Products ("CPMP") had recommended the granting of marketing authorization for DepoCyt®, marketed in Europe as DepoCyte®, for the treatment of neoplastic meningitis from lymphomas. In August 2001, the European Commission ratified the recommendation received from the CPMP by granting marketing authorization for DepoCyte® throughout the European Union for the treatment of neoplastic meningitis from lymphomas.

#### *Marketing Partners and Licensing*

In November 2002, the Company re-acquired the DepoCyt® marketing, distribution and sales rights for the United States from Chiron Corporation in return for an undisclosed cash payment, and for Canada from Paladin Labs Inc for a nominal sum. In December 2002, the Company licensed the North American rights to DepoCyt® to Enzon. Enzon paid a license fee of \$12 million. The Company will manufacture DepoCyt® and Enzon will purchase finished product at 35% of net sales, which will be reduced should a defined sales target be exceeded. The Company is also entitled to milestone payments based on the achievement of certain sales levels and the approval of additional indications.

Marketing and distribution rights for DepoCyte® for Europe and the Philippines were licensed to Elan Pharmaceuticals ("Elan") in June 2001 but following Elan's decision not to proceed with the planned establishment of an oncology sales force, SkyePharma reacquired these European rights during 2003 for an unspecified amount. In June 2003 the Company licensed exclusive marketing and distribution rights for DepoCyte® to Mundipharma for most European and Eastern European countries. The Company will manufacture DepoCyte® and supply it to Mundipharma associates at an agreed transfer price. Mundipharma will also pay SkyePharma an additional royalty on sales plus additional milestones. In February 2004, Mundipharma launched DepoCyte® in Europe.

In June 2001, the Company licensed the marketing rights for DepoCyt® in Japan and Taiwan to Nippon-Shinyaku. In 2003 the Company licensed marketing rights for DepoCyt® in Brazil to Pharmis Biopharmaceutica.

#### *Additional Territories and Indications*

The Company is currently conducting a Phase IV clinical trial, the results of which should provide data to support a claim for treatment of neoplastic meningitis associated with solid tumors in the United States and Europe.

#### *DepoDur*

The Company has developed DepoDur for the control of moderate to severe post-operative pain. The Company anticipates that DepoDur's main use will be in the control of post-operative pain in hospitalized patients undergoing surgical procedures requiring general or local anaesthetic such as major abdominal surgery, orthopaedic surgery and caesarean section. DepoDur is given as a single epidural injection in the peri-operative period and provides pain relief for up to 48 hours following surgery. DepoDur was approved by the FDA in May 2004 for the treatment of pain following major surgery and is licensed for the U.S. and Canada to Endo and to Medeus for Europe. The Company anticipates the launch of DepoDur in the United States in late 2004. If national approval in the UK is gained, the Company intends to seek approval in other European countries under the EU Mutual Recognition procedure.

#### *Clinical Development*

In December 1996, SkyePharma Inc. filed an investigational new drug application with the FDA to begin human studies of DepoDur (previously referred to as DepoMorphine) for the treatment of pain following major surgery. In December 1997, SkyePharma Inc. completed a Phase I dose-escalation study that assessed the safety and level of drug exposure in the blood of single doses of DepoDur administered to healthy volunteers.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

In February 2000, the Company announced that in Phase II clinical trials, DepoDur<sup>®</sup>, when given as a single pre-operative epidural injection in patients undergoing hip replacement surgery showed a statistically significant dose-related reduction in post-operative fentanyl usage and pain intensity scores for up to 48 hours as compared with patients receiving a pre-operative placebo. For patients requesting post-operative fentanyl, pain intensity at time of first request was rated "severe" in 57% of placebo patients but rated "severe" in only 21%, 9% and 4% in the patients dosed with 10mg, 20mg and 30mg of DepoDur<sup>®</sup> respectively.

In January 2001, the Company announced that it had started its Phase III clinical trials for DepoDur<sup>®</sup>. The last Phase III study was completed in March 2003. The clinical development program for DepoDur<sup>®</sup> involved four separate pain models involving nearly 1000 patients. In the two pivotal trials, in hip surgery and lower abdominal surgery, DepoDur<sup>®</sup> demonstrated sustained dose-related analgesia and achieved its primary endpoint (superiority over study comparators in terms of total demand for opioid analgesics after surgery) with a high degree of statistical significance. DepoDur<sup>®</sup> also achieved statistical significance on several secondary endpoints, such as patient perception of pain intensity and adequacy of pain relief. In two related Phase IIb trials, DepoDur<sup>®</sup> was significantly better than study comparators in a caesarean section study and approached statistical significance in a knee arthroplasty study. In the latter study, the primary endpoint was recalled pain intensity. DepoDur<sup>®</sup> did achieve a high degree of statistical significance in total demand for opioid analgesics after surgery, a secondary endpoint in the knee arthroplasty trial, but the primary endpoint in the three other studies.

In July 2003, the Company submitted the DepoDur<sup>®</sup> NDA to the FDA. In September 2003, the FDA formally accepted the NDA for filing. In November 2003, the Company submitted the DepoDur<sup>®</sup> marketing approval application to the UK Medicines and Healthcare Products Approval Agency. DepoDur<sup>®</sup> was approved by the FDA in May 2004 for the treatment of pain following major surgery.

### *Marketing Partners and Licensing*

In December 2002, the Company entered into a development and commercialization agreement under which Endo Pharmaceuticals Inc. received an exclusive license to the U.S. and Canadian marketing and distribution rights for two of the Company's patented development products, DepoDur<sup>®</sup> and Propofol IDD-D<sup>®</sup>, a product using the Company's IDD solubilization technology, with options for other development products in the area of pain management. In return, the Company received a \$25 million payment on signing in respect of DepoDur<sup>®</sup>. In addition, the Company may receive further milestone payments totaling \$95 million which include total milestones of \$10 million for DepoDur<sup>®</sup> through FDA approval. The total also includes a \$15 million milestone payment when net sales of DepoDur<sup>®</sup> reach \$125 million in a calendar year, and a \$20 million milestone payment when net sales of DepoDur<sup>®</sup> reach \$175 million in a calendar year. The Company will also receive a share of each product's sales revenue that will increase from 20% to a maximum of 60% of net sales as the products' combined sales achieve certain thresholds in any given year. The agreement provides for the parties to work together and complete the necessary clinical, regulatory and manufacturing work for regulatory approval of DepoDur<sup>®</sup> and Propofol IDD-D<sup>®</sup> in the United States and Canada. The Company will be primarily responsible for clinical development up to final FDA approval and for product manufacture, including all associated costs. Upon approval, Endo will market each product in the United States and Canada with the Company as supplier. Endo will be responsible for funding and conducting and post-marketing studies and for selling and marketing expenses.

In April 2004, the Company entered into a strategic marketing agreement with Medeus for the marketing and distribution of DepoDur<sup>®</sup> in Europe. The Company will receive a share of sales of DepoDur<sup>®</sup> that will increase from an initial 35% to a maximum of 50% of net sales provided certain sales thresholds are reached. The Company will also receive a payment on signing and will receive further future milestone payments on attainment of marketing approvals, commercial launches and sales targets; if all targets are met these payments will amount to over €100 million. The Company

will be responsible for the cost of manufacturing the product and for clinical development required to gain and maintain approvals throughout the expanded EU. Medeus will be responsible for the cost of all sales and marketing of the product, including pre-launch development and any further clinical studies (other than Phase IV studies for market development, for which the parties will collaborate).

*DepoFoam Injectable Products in Development*

The table below summarizes DepoFoam products currently under development. The stages of the development process, including definitions of the various stages, are explained under "Research and Development Development Process for Brand-Name Pharmaceuticals".

<b>Product (Active Compound)</b>	<b>Therapeutic category</b>	<b>Development Status</b>	<b>Collaborative Partner</b>
DepoBupivacaine (bupivacaine)	Post surgical/post injury pain	Phase I completed	SkyePharma
Interferon alpha-2b	Anti-viral/Oncology	Pre-clinical	GeneMedix

*DepoBupivacaine*

The Company is developing DepoBupivacaine, a DepoFoam formulation of the widely used local pain medicine bupivacaine for controlling post-surgical or post-injury pain. Pain associated with surgery or injury is often treated with local anesthetics. However, the usefulness of local anesthetics is frequently limited by their short period of effectiveness following administration which results in recurrence of pain and the need for repeated drug administration by a medical professional. One dose of DepoBupivacaine is expected to provide more than 24 hours of regional pain relief, compared with up to six hours following conventional bupivacaine administration.

SkyePharma Inc. has successfully encapsulated bupivacaine in a DepoFoam formulation ("DepoBupivacaine"). Initial studies have shown that DepoBupivacaine is released slowly at the site of injection, resulting in prolonged duration (more than 48 hours) of pain relief following a single-dose administration. The Company completed a Phase I clinical trial for DepoBupivacaine during 2001 and has completed a second Phase I study in 2003.

The Company believes that a DepoFoam formulation of a local anesthetic may complement DepoDur and that the DepoDur and local anesthetic formulations will give physicians improved drugs to manage post-operative pain.

Under the development and commercialization agreement with Endo for DepoDur and Propofol IDD-D signed in December 2002, Endo has an option to negotiate for commercialization rights for DepoBupivacaine in the U.S. and Canada when the Company successfully completes its Phase II trials, as well as other of the Company's products formulated using the DepoFoam technology successfully developed for the prophylaxis or treatment of pain.

*Interferon alpha-2b*

In June 2002, the Company signed a Joint Agreement with GeneMedix ("GeneMedix") plc to develop an extended release formulation of interferon alpha-2b using the Company's DepoFoam technology. Interferon alpha-2b is already accepted as a part of the standard therapy in the treatment of Hepatitis C and Hepatitis B infection, and as an adjunct to chemotherapy in certain forms of cancer. Therapeutic proteins are easily degraded inside the body. An extended release DepoFoam formulation of interferon alpha-2b has the possibility to deliver therapeutic doses of the protein in a controlled manner for a period up to 28 days from a single injection. This would represent a considerable benefit to patients with Hepatitis C whose current treatment may require injection of interferon alpha-2b up to every seven days. Following initial studies, the Company and GeneMedix are discussing the future of this collaboration. For a discussion of the terms of this agreement, see "Collaborative Arrangements Injectable".

*New Product Feasibility Programs*

The Company is also evaluating, with undisclosed corporate partners, DepoFoam<sup>®</sup> formulations of several additional compounds including macromolecules. These projects are all at the pre-clinical stage of development. The objectives of these programs are to:

determine whether candidate drugs can be successfully encapsulated in DepoFoam<sup>®</sup> formulations;

evaluate drug release characteristics in the lab and in animal tissue; and

conduct initial effectiveness and/or safety studies in animal models to demonstrate potential clinical utility and advantages of the DepoFoam<sup>®</sup> formulations.

*Biosphere<sup>®</sup> Technologies*

The Company believes that the Biosphere<sup>®</sup> injectable technology will complement its DepoFoam<sup>®</sup> sustained-release injectable expertise by providing additional delivery options for proteins and peptides. Proteins and peptides cannot be given orally because they will not survive passage through the digestive system. However, the short half-life of most protein and peptides means that injections usually need to be given frequently and, as injections are unpopular with patients, compliance tends to be poor.

The Biosphere<sup>®</sup> drug delivery system, acquired in May 2002, provides sustained-release of injectable proteins and peptides. The technology encapsulates the drug substance in highly purified starch in microscopic spheres that are then coated with a copolymer of lactic and glycolic acid. After injection, the coating and core erode and the drug content is released over a period that can be controlled from days to months. In contrast with conventional microspheres, the coating used in Biosphere<sup>®</sup> does not contain any drug so there is a low "burst" even at high drug loadings. The Biosphere<sup>®</sup> technology achieves encapsulation of protein drugs under controlled conditions that avoid exposure of the protein to destructive organic solvents that can often cause structural changes.

The first human administration of coated and uncoated starch Biosphere<sup>®</sup> microspheres containing no active drug took place in 2001. The study involved 16 subjects and no significant adverse reactions were reported. In February 2003 the Company announced that the Biosphere<sup>®</sup> technology had been successfully used to deliver a protein drug over an extended period of time. A paper in *Drug Delivery Systems & Sciences* (Vol. 2, No. 4, 103-109) by scientists from the Company's research unit in Malmo, Sweden describes pre-clinical studies on the release of human growth hormone over a period of two weeks from a single injection. In the study, the human growth hormone was encapsulated with high efficiency and released evenly throughout the period. Importantly the gentle encapsulation process and the inert conditions within the Biosphere<sup>®</sup> particles preserved protein structure and function. A Biosphere<sup>®</sup> formulation of human growth hormone was studied in a Phase I clinical trial that was successfully completed at the end of 2003. In addition to the human growth hormone, the Company is also evaluating Biosphere<sup>®</sup> formulations of other proteins and peptides.

***Inhalation***

*Inhalation Technologies*

The Company is developing advanced inhalation drug delivery technologies that are designed to deliver medicines via a patient's lungs without relying on aerosol inhalers powered by CFC-based propellants, which are considered environmentally harmful. The 1997 Montreal protocol signed by more than 140 countries aims to eliminate the manufacture, use and sale of CFC propellants by 2005. This pressure for the phasing out of CFCs has led to an increased focus on the development of both non-CFC MDIs and DPIs. The Company is currently working with two types of inhalation drug delivery systems: non-CFC MDIs using hydro-fluoro-alkanes ("HFA") as a



propellant and DPIs that require no propellant and are breath-actuated. In its MDI development work, the Company focuses on the formulation of drugs for use in MDIs manufactured by third parties. In its DPI development work, the Company focuses both on the development of the device and on the formulation of drugs for use with the device.

In both its MDI and DPI development work, the Company's objective is to maximize the efficiency of the delivery system while addressing commercial requirements for reproducibility, formulation, stability, safety and convenience. The Company has assembled a team of researchers with substantial experience in both powder and aerosol science and is applying this expertise to develop proprietary techniques and methods that it believes will produce stable and reproducible dry powder and aerosol formulations. To achieve this goal, the Company is combining an understanding of lung biology, aerosol science, chemical engineering and mechanical engineering.

#### *MDI Technologies*

Metered dose aerosol inhalers, the most widely used systems for inhalation drug delivery, have been in existence for more than 40 years and are primarily used to deliver asthma medications and other small molecule drugs to the lung, although significant advances have been made in recent years in the delivery of large molecule drugs, such as peptides and proteins, via the lung. The drugs are typically packaged in a portable canister as a suspension or solution in a volatile propellant. The primary technical challenge in developing a non-CFC MDI results from the fact that the two most widely used non-CFC propellants, HFA 134a and HFA 227, behave differently from CFC gases because of their physicochemical characteristics. This has resulted in a need for a complete reengineering of the MDI device rather than a simple substitution. Among other things, this means that the mechanical components of the MDI device, especially the valves and gaskets, must be completely reformulated to work properly with non-CFC gases. The Company's work in this area has resulted in a high level of expertise in the evaluation of valves and gaskets utilized in the MDI device. The Company is currently developing aerosol formulations of a range of generic or off-patent drugs for the treatment of asthma. In its formulation work, the Company is working with both the HFA 134a and HFA 227 propellants.

#### *DPI Technologies*

Dry powder inhalation technology has emerged as an effective means of delivering asthma medications to the pulmonary system without the use of CFC propellants. DPIs rely on the patient's own lung power to deliver a fine dry powder suspension to the lung. DPI drug compounds are formulated in solid form and packaged in portable containers. Most DPIs currently on the market provide medicine in a pre-metered single dose form, such as a gelatine capsule or blister pack. Under the brand name "SkyeHaler", the Company is developing a DPI with a drug reservoir with the capacity to deliver up to 300 doses.

The primary technical challenge in developing a DPI device is to design a product that offers accurate and uniform dosing at variable flow rates of inhalation. Although additional testing remains to be performed, the Company believes that it has solved this problem by designing and incorporating valves in its DPI that make delivery flow-rate independent at inhalation rates of between 25 and 60 litres per minute. The Company's DPI is fully breath-actuated and offers an easy-to-use mechanism that is capable of delivering uniform doses. In addition, the device benefits from a counter that keeps track of how many doses remain in the device.

Each drug designed for use with a DPI poses different formulation challenges due to varying physical and chemical characteristics and dosing requirements. These challenges require significant optimization work for each drug. The Company has assembled a team with substantial experience in formulation, dry powder science and aerosol science and is applying this expertise to develop proprietary techniques and methods that it believes will produce stable, fillable and dispersible dry powder drug formulations. Through its development work, the Company is developing an extensive body of knowledge of dry powder formulations, including knowledge relating to powder flow

characteristics and solubility within the lung, as well as physical and chemical properties of various excipients.

The Company believes that its DPI benefits from the following features:

*Flow Rate Independent.* The Company's DPI offers accurate and uniform dosing at variable flow rates of inhalation of between 25 and 60 litres per minute.

*Breath Actuated.* The Company's DPI relies on the patient's own lung power to deliver a fine powder suspension to the lung.

*Uniform Delivery.* The Company's DPI offers an easy-to-use mechanism to deliver consistent and uniform doses to the lung.

*Dose Counter.* The Company's DPI incorporates an easy-to-read dose counter that keeps track of how many doses remain in the device.

The Company is continuing to seek additional collaborative partners to further develop and commercialize its inhalation drug delivery technologies. The Company's strategy is to enter into development contracts with established pharmaceutical companies. In entering into collaborative arrangements, the Company's goal is to cover all or a large part of its research and development costs and receive milestone payments upon the achievement of specified objectives. The Company would expect to receive royalties from its partners based on sales of products incorporating the Company's pulmonary drug delivery technologies.

#### *Approved Inhalation Products*

##### *Foradil® Certihaler®*

In November 1998, the Company and Novartis agreed to jointly develop a new formulation of Novartis' Foradil® asthma drug using the Company's SkyeHaler, together referred to as the Foradil® Certihaler®. For a discussion of the terms of the agreement, see "Collaborative Arrangements - Inhalation".

Formoterol, the active ingredient in the Foradil® Certihaler®, is a long-acting beta-agonist bronchodilator, which combines a rapid onset of action (within 1 - 3 minutes) with a long-lasting bronchodilation of 12 hours. This feature offers large benefits for all patients who suffer from obstructive lung diseases. Formoterol is licensed by Novartis from Yamanouchi Pharmaceuticals. Foradil® is currently marketed in over 60 countries and in 2003 Novartis reported sales outside of the U.S. of \$280 million. The Certihaler® DPI contains 60 doses giving patients the convenience of 30 days of therapy in a single inhaler.

In October 2002, Schering-Plough obtained exclusive U.S. distribution and marketing rights to all Foradil products from Novartis. Schering-Plough currently markets Foradil® Aerolizer (formoterol fumarate inhalation powder), a single-dose inhalation device. Novartis retains international rights to the Foradil® product line. This licensing did not affect the Company's commercial agreement on royalties or manufacturing with Novartis.

On December 20, 2002, the Company announced the submission by Novartis of a NDA for the Foradil® Certihaler® to the FDA and to health authorities in the European Union, for review on a country-by-country basis. In October 2003 the FDA issued an approvable letter for the Foradil® Certihaler®. This means that the product can be approved by the FDA subject to resolution of certain outstanding issues. In March 2004 the Company announced that the Certihaler® had received its first European approval when the Swiss pharmaceutical regulatory authority approved the Foradil® Certihaler®. The Certihaler® has been subsequently approved in Finland and Austria.

*Inhalation Products in Development*

The table below summarizes inhalation products currently under development. The stages of the development process are explained under "Research and Development - Development Process for Brand-Name Pharmaceuticals".

<b>Product</b>	<b>Therapeutic Category</b>	<b>Development Status</b>	<b>Inhalation System</b>	<b>Collaborative Partner</b>
Pulmicort® MDI	Asthma	Phase III	HFA-MDI	AstraZeneca
HFA-formoterol	Asthma	Phase II	HFA-MDI	SkyePharma
QAB 149	Asthma/COPD	Phase I completed	DPI	Novartis
Formoterol Combi	Asthma	Phase I	HFA-MDI	SkyePharma

*Pulmicort® MDI*

In December 2001, the Company signed exclusive agreements with AstraZeneca to develop the next generation of AstraZeneca's Pulmicort® (budesonide) MDI for the European market. The Company will apply one of its inhalation delivery technologies using HFA as propellant to replace CFC's in the currently marketed MDIs. For a discussion of the terms of this agreement, see "Collaborative Arrangements Inhalation". The Company has already developed an internal formulation of budesonide, the active ingredient in Pulmicort®, that is pharmaceutically stable and suitable for use in an HFA-MDI. Phase II clinical studies on the AstraZeneca formulation have been completed and successfully demonstrated equivalence with the CFC aerosol version. Phase III clinical studies in Europe commenced in June 2003.

*HFA-formoterol*

The Company's HFA formulation of the long-acting beta-agonist formoterol, "HFA-formoterol", will be used in MDIs to treat asthma. The Company's Phase II trial data has confirmed that its HFA aerosol inhaler is equivalent to the dry powder version of formoterol in terms of effect on patient lung function. HFA-formoterol has completed Phase II clinical studies and is expected to enter Phase III clinical trials in the second half of 2004.

*QAB 149*

In December 2003, the Company announced an agreement with Novartis to jointly develop a new product for the treatment of asthma and COPD. The product will combine QAB 149, Novartis' novel long-acting bronchodilator that is currently in Phase II trials for asthma, with two SkyePharma technologies: the SkyeHaler and SkyeProtect, a powder formulation that protects the drug from atmospheric moisture to ensure product stability and dose-to-dose reproducibility. The product has successfully completed a technical feasibility study. The Company received an initial payment on signature of the agreement and, if the co-development project progresses successfully, Novartis will also make future payments on attainment of development milestones and will pay SkyePharma royalties on eventual sales.

*Formoterol-Combi*

The Company is developing a fixed-dose combination of formoterol, the long-acting beta-2 agonist, with fluticasone, an inhaled corticosteroid, to be used in MDIs to treat asthma. The combination product, known as "flutiform", completed Phase I trials in 2004. The product is expected to enter Phase II in the second half of 2004.

## *Topical*

### *Topical Technologies*

#### *HA-Based Technologies*

The Company's "HA"-based technologies were acquired from Cade Struktur. They are topical drug delivery technologies based on HA, a natural polymer, which is designed to maintain efficacy and localize the delivery of drugs to the skin for the treatment of a variety of skin disorders. HA is a long-chained polysaccharide that is a major constituent surrounding cells in most animal tissues. In solution in water, HA's coiled structure acts as a net which can entrap a wide variety of drug compounds. HA is attracted to and adheres to specific receptors on cell membranes which can be found in increasing numbers at sites of damage and disease in the body. This means that drugs can potentially be targeted to and held at the site where the drug is needed. HA's safety profile, its ability to carry drugs and its potential targeting characteristics make it an excellent vehicle for drug delivery. The Company anticipates that by enhancing the delivery of a specific drug, treatment with HA formulations might require less drug compared with treatment with the drug administered by itself. As a result, the Company believes formulations employing HA based technologies may result in decreased systemic side effects or enhanced therapeutic effect.

#### *Crystalip*

Certain rights to the Crystalip technology were licensed from Bioglan in December 2000. The remaining rights were acquired by the Company in May 2002. Crystalip enhances stability of drugs by embedding them in lipid crystals. Suitable for hydrophilic or hydrophobic drugs, the drug is released as the lipid melts at skin temperature. The major advantage of Crystalip comes from its versatility, as it can be formulated as a spray, lotion, cream or paste. Additionally, it can stabilize lipophilic and hydrophilic actives, provide photostabilization, and, due to its anti-microbial effect, can be free from preservatives leading to a low risk of toxic or allergic reactions. There are no direct competitors to Crystalip in providing both stabilization of lipophilic and hydrophilic drugs combined with an anti-microbial effect.

#### *DermaStick*

The DermaStick technology was acquired from Bioglan in two stages, together with the Crystalip technology. DermaStick presents the active ingredient in a wax stick, which facilitates controlled application to affected skin. A major advantage of DermaStick over existing stick technologies is that it avoids the problem of poor homogeneity of stick formulations. Poor homogeneity is experienced because the active is suspended in the vehicle, and during the solidification process the suspended active is allowed to sediment. The DermaStick avoids this issue by holding the active in solution and thereby allowing manufacture of homogeneous sticks.

#### *ES-Gel*

The ES-Gel technology was acquired from Bioglan in two stages, together with the Crystalip and DermaStick technologies. ES-Gel is a semi-solid formulation producing enhanced solubility of drugs and providing substantially increased bioavailability by the transdermal route. The system will primarily compete with transdermal patch technologies. Other than the avoidance of the need for a patch, the major advantage is ES-Gel's ability to deliver low water soluble compounds through the skin and to do this without the use of penetration enhancers. The resultant products may also be significantly lower cost compared with patches and most other transdermal delivery systems.

### *Approved Topical Products*

#### *Solaraze®*

The first approved drug product using the Company's HA-based technology is Solaraze®. Solaraze® is a topical gel used to treat actinic keratosis, a pre-cancerous skin condition caused by

over-exposure to the sun. It is a formulation of HA and the non-steroidal anti-inflammatory drug diclofenac. Solaraze® has been shown to be an effective topical product for actinic keratosis. Compared with other actinic keratosis treatments, Solaraze® is non-invasive, non-scarring and is well tolerated by patients.

In July 1997, Solaraze® received regulatory approval for marketing in the United Kingdom. Subsequently, in May 1998, Solaraze® was approved for marketing in Germany, Sweden, Italy, France and Canada. In October 1998, the Company submitted an NDA for the marketing of Solaraze® in the United States, which was filed by the FDA in December 1998. The Company received FDA approval for this product in October 2000.

In March 2000, the Company entered into an agreement with Bioglan for the manufacture, marketing and distribution of Solaraze® in Europe for an upfront licensing fee and royalty payments. In December 2000, the Company entered into a further agreement with Bioglan for the license of marketing rights to the United States, Canada and Mexico for Solaraze®, for which Bioglan paid a \$14 million fee and agreed to pay further significant milestone payments upon commercialization of Solaraze®.

In December 2001, the Company agreed to the transfer of rights to market Solaraze® in the United States, Canada and Mexico from Bioglan to Quintiles. Under this agreement, Bioglan received £15 million from Quintiles in return for the U.S., Canadian and Mexican rights to market and sell Solaraze®. In addition, Quintiles paid SkyePharma \$5 million and Bioglan agreed to pay SkyePharma \$12.5 million in settlement of monies owing under the license agreements between the two companies for the sales and marketing of Solaraze® in United States, Canada and Mexico. Quintiles subsequently launched Solaraze® in the United States in January 2002. On February 21, 2002, the affairs of Bioglan were placed into administration. On May 13, 2002, following negotiations with the Administrators of Bioglan, SkyePharma announced an agreement to transfer all rights to market Solaraze® in Europe to Shire for a total consideration up to £15 million, plus royalties on European sales. Of this total consideration, £2.1 million is contingent on conditions, including Solaraze®'s launch in certain European countries.

On June 9, 2004, Quintiles announced that it had reached agreement to sell assets relating to its specialty dermatology products company, Bioglan Pharmaceuticals, to Bradley Pharmaceuticals, Inc. ("Bradley") in a transaction valued at \$183 million in cash, plus direct costs for transferred inventory. Completion of the agreement is subject to satisfaction of customary conditions and regulatory requirements. The assets sold to Bradley include the marketing rights for the United States with respect to Solaraze®. Pursuant to the Company's agreement with Quintiles, transfer or assignment of these rights may require the Company's consent depending upon the structure of the agreements between Quintiles and Bradley. The Company is in discussion with Quintiles in respect of such consent.

In September 2002, the Company entered into a reciprocal licensing agreement with Meditech concerning the marketing of Solaraze® in certain Pacific Rim territories. The Company had acquired rights to Solaraze® in 1999 from the administrators of Cade Struktur, excluding those relating to certain Pacific Rim territories which were owned by Meditech under a pre-existing agreement with Cade Struktur. Under this agreement, the Company reacquired these territorial rights to Solaraze® from Meditech in return for an upfront payment, a milestone payment payable on regulatory approval of the product in Australia or New Zealand, and a royalty on sales. Through this agreement, the Company gained the exclusive right to manufacture and market or sublicense Solaraze® in Australia, New Zealand, Singapore and Malaysia whilst Meditech obtained equivalent rights in China, Taiwan, Indonesia and the Philippines, none of which were included in Meditech's original agreement with Cade Struktur. Each party will receive an identical royalty on sales made by the other party in its allocated territory.

In December 2002, the Company licensed to Shire the exclusive rights to manufacture, distribute and sell Solaraze® in Australia, New Zealand, South Africa and certain other countries in the Pacific Rim not included in the Company's license to Meditech. In return for these rights, the

Company will receive up to a total of £2.2 million pounds comprising an undisclosed upfront payment and additional milestone payments contingent on the product's successfully completing a Phase III clinical study in Australia and receiving regulatory approval in the licensed territories. The Company will also receive royalties on net sales and milestones as sales exceed certain levels.

#### *Topical Products in Development*

In addition to Solaraze®, the Company had been developing Hyclinda, a topical gel to treat acne, a formulation of acyclovir in ES-Gel in conjunction with Sakai and various other early stage products under its Crystalip, DermaStick and ES-Gel systems.

#### *Licensing*

On April 29, 2004 the Company announced that it had licensed the rights to its dermatology assets, which account for substantially all of its topical drug delivery technologies, for those territories that are not covered by existing licenses, to Trigenesis. The rights relate to three marketed drugs, including Solaraze®, rights to six pipeline products, including Hyclinda and Acyclovir, and six proprietary and complementary delivery technologies, including HA-based technologies, Crystalip, Dermastick, ES-Gel, Dissocubes and Solid Lipid Nanoparticles. Under the agreement, Trigenesis is obligated to exploit the dermatology assets covered by the license and to continue the development of those drug candidates that are currently at the pipeline stage. Trigenesis has also assumed the majority of SkyePharma's existing obligations to third parties with respect to the development of these drug candidates. All rights granted by the Company to licensees under existing licenses remain unaffected by the agreement. In addition, the Company has retained the right to use the technologies subject to the license for the development of a number of new chemical entities in the dermatology area and, in certain cases, also for non-dermal applications.

The Company received a payment on signing and for each of the six pipeline products may receive additional milestones on completion of Phase III trials and on approval. If all six products reach the market in the United States and Europe, total milestone payments (including the payment on signing) will be in excess of US\$20 million. The Company will also receive a 10% royalty on sales of these products by Trigenesis and 35% of any sub-license income. Trigenesis will be obligated to develop the pipeline products and to exploit the delivery technologies and will also assume certain of the Company's existing obligations to third parties involved in development.

Subsequent to the completion of Trigenesis agreement, Trigenesis announced on May 6, 2004, that it was being acquired by Dr Reddy's, an Indian pharmaceutical company, which will assume all the obligations of Trigenesis.

#### *Solubilization*

##### *Solubilization Technology*

Solubility of drugs is an essential factor for all drug delivery systems, independent of the route of administration. Poor solubility leads to a range of problems including poor bioavailability, increased toxicity, variability of absorption when taken with food and poor efficacy. The Company believes that a large number of existing marketed drugs and newly synthesized compounds have solubility problems. The acquisition of nano-particulate technology from Medac and the IDD technology from SkyePharma Canada provides the Company with access to important enabling technologies for the enhanced delivery of poorly water-soluble drugs.

Nano-particulate technology aims to improve a drug's solubility by reducing the size of the particles. It has been demonstrated in laboratory testing that the saturation solubility of many drugs can be improved by reducing particle size below one micron in diameter. The nano-particles are produced via a process of homogenization whereby a therapeutic compound dispersed in a solvent or a compound carrier system is subjected to size reduction forces in a homogenizer. A

homogenizer is a device where material is pushed through a narrow chamber at very high pressure. The process breaks down the particles of the compound and generates particles in the nanometer size range.

The nano-particulate technology acquired from Medac was originally developed by a team of researchers at the Free University of Berlin in the early 1990s and was subsequently licensed to Medac which pursued the development of the technology. The nano-particulate technology acquired from Medac consists of three separate techniques:

Nano-suspensions, a dispersion of pure drug without any matrix including the Dissocubes technology;

Solid Lipid Nano-particles, solid solutions of drugs in a lipid matrix; and

Solid Polymer Nano-particles, solid solutions of drugs in a solid polymer matrix.

The IDD technology platform acquired with the acquisition of SkyePharma Canada has been developed since the early 1990s with over \$50 million having been invested in the technology and development of a proprietary product pipeline. To date, no products using the IDD technology have been approved. The IDD technology incorporates the following methods:

MicroParticle (IDD-P ), phospholipid stabilized sub-micron to micron sized water-insoluble drug particles. This approach can be used for a wide range of insoluble drugs to be administered via the oral, topical, injectable, implantable or inhaled routes; and

MicroDroplet (IDD-D ), phospholipid stabilized sub-micron to micron sized emulsions of water-insoluble drug substances. This approach is available also to a restricted range of drugs, limited by solubility in biocompatible oils, administered by the injectable route.

The IDD technology acquired with SkyePharma Canada is complementary to the Company's existing nano-particulate technology acquired from Medac, and, therefore, the Company expects to be able to provide customers with a wider range of patented solubilization technologies. It is intended that the SkyePharma solubilization technologies will also be used to complement and enhance the Company's other drug delivery systems.

As part of the license of its dermatology assets to Trigenesis on April 29, 2004 the rights for Dissocubes and Solid Lipid Nanoparticles for the topical therapeutic treatment of dermatological diseases and disorders were licensed to Trigenesis.

#### *Advantages of solubilization technologies*

The Company believes that its solubilization technologies acquired from Medac and SkyePharma Canada offer a number of potential advantages over other solubilization technologies being developed by pharmaceutical and biotechnology companies. These include the following:

*A variety of solutions.* The SkyePharma technology encompasses five different approaches: nano-suspensions, solid lipid nano-particles and solid polymer nanoparticles, MicroParticle and MicroDroplet. This variety of approaches provides the Company with a number of different methods to address solubility problems.

*Simplicity of manufacturing process.* All particles are produced on the same relatively simple equipment, which may reduce the investment cost and complexity of the manufacturing operation.

*Rapid manufacturing process.* The homogenization part of the manufacturing process typically takes 1 to 2 hours which is significantly shorter than other processes used by competitors.

*Narrow particle size range.* The particles produced are within a narrow size range.



## Edgar Filing: SKYEPHARMA PLC - Form 20-F

### *Solubilization Products in Development*

The table below summarizes products currently under development based on the solubilization technologies. The stages of the development process are explained under "Research and Development – Development Process for Brand-Name Pharmaceuticals".

<b>Product</b>	<b>Therapeutic Category</b>	<b>Development Status</b>	<b>Solubilization System</b>	<b>Collaborative Partner</b>
Fenofibrate	Cardiovascular	Filed	IDD-P	SkyePharma
Propofol IDD-D	Anesthesia/Sedation	Phase II completed	IDD-D	Endo
Busulfan	Oncology	Phase II	IDD-P	SuperGen
Multiple	Undisclosed	Feasibility	IDD-P	Baxter

#### *Fenofibrate*

The Company has been developing an improved formulation of fenofibrate in partnership with an undisclosed pharmaceutical company. During 2003 the Company and its partner re-negotiated the terms of their agreement and the Company re-acquired rights to the product for an unspecified amount. Fenofibrate is a lipid-lowering drug launched by Abbott as Tricor in the United States in 1998. The IDD formulation is a lower dose product providing blood levels similar to the 200mg currently marketed form. A response to an approvable letter from the FDA was filed in March 2004.

#### *Propofol IDD-D*

Propofol is the active ingredient in AstraZeneca's Diprivan, a leading injectable anesthetic, which achieved sales in 2003 of \$458 million. The Company is developing an improved formulation of propofol using its IDD-D technology. Patents on Diprivan began to expire in 2000. Despite incorporation of an anti-microbial preservative, Diprivan has problems with micro-organism growth if the product is not properly handled and also may cause the build up of fats in the body. The Company believes the IDD-D formulation is inherently anti-microbial and offers improvement in both these areas. Propofol IDD-D completed Phase II trials during 2003 with a target launch date, on successful completion of clinical trials, in 2006.

In December 2002, the Company entered into a development and commercialization agreement under which Endo Pharmaceuticals received an exclusive license to the U.S. and Canadian marketing and distribution rights for two of the Company's patented development products, DepoDur, an injectable product, and Propofol IDD-D, with options to negotiate for other development products in the area of pain management. For a discussion of the terms of the agreement, see "Collaborative Arrangements – Solubilization".

Propofol IDD-D has completed its Phase II clinical trial. The study, involving 79 female patients undergoing laparoscopic gynaecological surgery, was designed to show clinical effect of Propofol IDD-D versus Diprivan, a currently marketed version of 1% propofol. The study results provided evidence of comparable pharmacokinetics, efficacy and safety of the two formulations which will need to be confirmed in Phase III trials. In April 2004 the Company announced that it had successfully completed the review of the Phase II trial results of Propofol IDD-D with the FDA. SkyePharma and Endo have agreed upon the Phase III trial programme and expect Propofol IDD-D to commence Phase III trials in late 2004. The Phase III study will involve over 700 patients and is intended to support three target indications: general anesthesia in adults, monitored anesthesia care in adults and use in the intensive care unit for the sedation of intubated, mechanically ventilated adults.

#### *Busulfan*

The Company has developed an injectable formulation of Busulfan, for bone marrow transplants in pediatrics, in partnership with SuperGen, Inc. ("SuperGen"), using its IDD-P

technology. Busulfan is currently marketed by SuperGen in oral form. The new formulation does not contain dimethyl acetamide ("DMA"), does not require refrigeration and is in Phase II trials. The Company has not been given any indication by SuperGen in the last year that this project is in active development.

#### *Baxter*

The Company has an exclusive agreement with Baxter to collaborate on the use of the IDD technology for the formulation of injectable New Chemical Entity ("NCE") medications. Baxter will work with its pharmaceutical company clients to develop injectable formulations for insoluble medications utilizing the IDD technology and its expertise in formulating and manufacturing injectable drugs. One of the most challenging issues in the development of many pharmaceutical products is formulating a water-insoluble NCE a drug molecule that cannot be dissolved in water so that it can be administered to patients in an injectable form. Under the terms of the agreement, the Company will receive milestone payments from Baxter based on certain events leading to the commercialization of the first product under the collaboration. In addition, the Company will receive a proportion of license fees, milestone payments and royalties on net sales of the IDD formulated injectable medications developed by Baxter for Baxter's global pharmaceutical company partners. Baxter has exclusive manufacturing rights to these products. Where the Company develops products for Baxter's partners, the Company will pay to Baxter a proportion of the milestones and royalties earned. In 2003, the agreement with Baxter was extended to incorporate the Medac nano-particulate technology.

#### *New Product Feasibility Programs*

In addition to the above described products, the Company has disclosed alliances with Schering Plough Corporation and has internal development products at early stages of development.

### **Collaborative Arrangements**

#### *Overview*

The Company has collaborative arrangements with each of its pharmaceutical partners, the terms of which vary considerably. Pursuant to these arrangements, the Company's partners typically fund all or a large part of the research and development expenses incurred in the development of new formulations of their products. Most of the Company's development contracts either provide for a flat fee for the Company's research and development efforts or provide for an agreed research and development budget. Some agreements have involved equity investments in the Company by the Company's partners. In negotiating contracts with its partners, the Company's strategy generally has been to cover its costs in the research and development process. Substantially all potential profits are expected to be generated by royalty payments or manufacturing fees for successfully developed and marketed products. In some cases, the partners have agreed to make specified payments to the Company upon the achievement of certain technical or commercial milestones, which may be deducted from future royalty payments for successfully developed and marketed products.

In return, the Company gives each of its partners an exclusive license to market the products incorporating the Company's technologies. In some cases the licenses are worldwide. In others they are limited to specific territories. In all cases, however, partners are free to sublicense the technologies, although the Company's consent may be required and royalties on all sales must be paid to the Company. In addition, the majority of the collaborative agreements do not prohibit the Company from developing formulations of competitive products. In some cases, however, the Company will agree not to develop formulations of specified compounds for an agreed period of time. Most of the agreements do not prohibit partners from developing, either internally or in collaboration with the Company's competitors, controlled-release versions of the contract products.

The Company's collaborative partners generally take responsibility for conducting clinical trials and for preparing and pursuing all necessary regulatory approvals although more recently the Company has taken responsibility for managing clinical trials in some collaborations. The Company may assist its partners in the conduct of such trials and the preparation of regulatory filings, but its partners ultimately control the process, including the selection of the jurisdictions in which regulatory approval will be sought, if at all.

The collaborative agreements do not typically obligate the partners to market any successfully developed and approved products. The Company does not have any control over whether and to what extent a partner will elect to commercialize a product. A client may choose not to market a product for reasons wholly independent of the Company's technologies. In most cases, if a client does not proceed to market the product once it has been successfully formulated and approved, the Company will not receive any additional income in respect of the product. In some more recent collaborations, however, contracts have included certain commitments for the Company's partners to market the product or to pay a minimum royalty in lieu of sales of the product.

During the formulation and development stages, the Company's partners are generally free to terminate the collaborative relationship at any time and for any reason.

### *Oral*

The Company is currently receiving significant royalty revenues under two collaborative arrangements for its Geomatrix<sup>®</sup> technology: Xatral<sup>®</sup> OD/Uroxatral<sup>®</sup> and Paxil CR<sup>®</sup>. Under the terms of these agreements, each of the development partners bore all of the costs of research and development according to an agreed budget and are obligated to pay the Company continuing net royalties of between 1.5% and 5% of net sales. In return, the Company granted the development partners exclusive licenses to use the Geomatrix<sup>®</sup> technology in these products throughout the world. The license agreement for Xatral<sup>®</sup> OD/Uroxatral<sup>®</sup> was signed in May 1999 with Sanofi-Synthelabo. The license agreement for Paxil CR<sup>®</sup> was signed in March 1996 with SmithKline Beecham plc (now part of GlaxoSmithKline). For further discussion of the license agreement for Paxil CR<sup>®</sup>, see "Item 10: Additional Information - Material Contracts".

The only collaborative arrangement involving Geomatrix<sup>®</sup> technology in which the Company is responsible for conducting clinical trials is the development and licensing agreement for a once-daily version of Requip<sup>®</sup> (ropinirole) with GlaxoSmithKline, which was entered into in September 1999 with SmithKline Beecham (now part of GlaxoSmithKline). Under the terms of the agreement with GlaxoSmithKline the Company is responsible for all development activities for Requip<sup>®</sup> oral controlled release tablets up to regulatory filing, in collaboration with GlaxoSmithKline. As part of the agreement, GlaxoSmithKline made an equity investment of £4.9 million in the Company and will pay milestone payments at intervals up to product approval, including an upfront payment. In December 2001 and June 2003, the Company and GlaxoSmithKline amended the 1999 license for Requip<sup>®</sup> to take account of additional activities that had been undertaken by SkyePharma. Under the terms of the amendments, the timeline of certain milestone payments was renegotiated together with additional development revenues to reimburse SkyePharma for the additional activities. On commercialization of once-daily Requip<sup>®</sup>, the Company will receive royalties on future product sales. GlaxoSmithKline will take responsibility for preparing and pursuing all necessary regulatory approvals. The once-daily version commenced Phase III clinical trials in June 2003.

The Company has a development and license agreement for Dilacor<sup>®</sup> XR, signed in 1998 with Rorer, a member of the Rhône Poulenc Rorer Group (now part of Aventis Pharma). In 1997, Rorer granted to Watson Laboratories, Inc. (with the consent of the Company) exclusive rights to market, advertise, promote, sell and distribute Dilacor<sup>®</sup> XR. The grant of rights to Watson Laboratories does not affect any entitlements of the Company or any of the material terms of the collaborative arrangement. The Company no longer receives royalties under this agreement.

In addition, in 2002 the Company entered into a technology access, license and development agreement with e-nutriceuticals, Inc for the use of the Company's Geomatrix technology. In connection with the agreement the Company was issued convertible preferred stock. In August 2003, e-nutriceuticals merged with Vital Living Inc ("Vital Living") and as a result of the merger SkyePharma acquired 14,204,548 common shares in Vital Living. During 2003, the Company acquired additional preferred shares, notes and warrants that in total, assuming conversion, would give the Company a 28.1% stake in Vital Living's ordinary share capital. This investment is recorded within fixed asset investments.

### *Injectable*

In July 1997, SkyePharma Inc. entered into a marketing and distribution agreement with Pharmacia Corporation. Under the agreement, Pharmacia Corporation acquired rights to market and sell DepoCyt® in countries outside the United States. In February 2000, the Company recovered the rights to DepoCyt® for Japan and Canada. In June 2000, Pharmacia Corporation notified the Company that it was terminating the 1997 Marketing and Distribution Agreement. Subsequently, Pharmacia Corporation assigned the European marketing application to the Company and the Company continued to pursue the European marketing approval. In April 2001, the Company received notification that the CPMP had recommended the granting of marketing authorization for DepoCyt®, for the treatment of neoplastic meningitis from lymphomas. The CPMP's recommendation was forwarded to the European Commission for ratification. In June 2001, the Company licensed the marketing and distribution rights for DepoCyt® in Europe and the Philippines to Elan. In August 2001, the European Commission approved DepoCyt® for marketing throughout the European Union.

In March 1994, SkyePharma Inc., then known as DepoTech, entered into a collaboration with Chiron to develop and commercialize DepoCyt® for use in the treatment of neoplastic meningitis. The Chiron agreement granted Chiron rights to market and sell DepoCyt® in the United States. In June 2000, the Company licensed the marketing and distribution rights for DepoCyt® in Canada to Paladin Inc.

In November 2002, the Company re-acquired DepoCyt® marketing, distribution and sales rights for the United States from Chiron Corporation in return for an undisclosed cash payment, and for Canada from Paladin Labs Inc for a nominal sum. In December 2002, Enzon licensed the North American rights to DepoCyt® from the Company for a license fee of \$12 million. The Company will manufacture DepoCyt® and Enzon will purchase finished product at 35% of net sales, which will reduce should a defined sales target be exceeded. The Company is also entitled to milestone payments based on the achievement of certain sales levels and the approval of additional indications. At December 31, 2002, the Company had a promissory note with Chiron of \$1 million which formed part of the consideration for the reacquisition of the DepoCyt® marketing, distribution and sales rights. The promissory note is repayable in 2004 and bears interest at LIBOR plus 3%.

Marketing and distribution rights for DepoCyt® for Europe and the Philippines were licensed to Elan Pharmaceuticals ("Elan") in June 2001, but following Elan's decision not to proceed with the planned establishment of an oncology sales force SkyePharma reacquired these European rights during 2003 for an unspecified amount. In June 2003 the Company licensed exclusive marketing and distribution rights for DepoCyt® to Mundipharma for most European and Eastern European countries. Under the terms of the agreement, Mundipharma paid the Company €4.25 million (\$4.9 million) on signature plus additional milestone payments that may amount in total to €10.75 million (\$12.3 million). The Company will manufacture DepoCyt® and supply it to Mundipharma associates at an agreed transfer price. Mundipharma will also pay SkyePharma an additional royalty on sales plus additional milestones. In February 2004 Mundipharma launched DepoCyt® in Europe.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

In June 2001, the Company licensed the marketing rights for DepoCyt® in Japan and Taiwan to Nippon-Shinyaku. In 2003 the Company licensed marketing rights for DepoCyt® in Brazil to Pharmis.

In December 2002, the Company entered into a development and commercialization agreement under which Endo Pharmaceuticals Inc. received an exclusive license to the U.S. and Canadian marketing and distribution rights for two of the Company's patented development products, DepoDur and Propofol IDD-D, a product using the Company's IDD solubilization technology, with options to negotiate for other development products in the area of pain management. In return the Company received a \$25 million payment on signing in respect of DepoDur. In addition, the Company may receive further milestone payments up to \$95 million which include total milestones of \$10 million for DepoDur through FDA approval. The total further comprises a \$15 million milestone payment when net sales of DepoDur reach \$125 million in a calendar year, and a \$20 million milestone payment when net sales of DepoDur reach \$175 million in a calendar year. The Company will also receive a share of each product's sales revenue that will increase from 20% to a maximum of 60% of net sales as the products' combined sales achieve certain thresholds in any given year. The agreement provides for the parties to work together and complete the necessary clinical, regulatory and manufacturing work for regulatory approval of DepoDur and Propofol IDD-D in the United States and Canada. The Company will be primarily responsible for clinical development up to final FDA approval and for product manufacture, including all associated costs. Upon approval, Endo will market each product in the United States and Canada with the Company as supplier. In respect of the first product launched under the agreement, the Company will pay Endo a fixed contribution in relation to marketing activities undertaken by Endo in respect of the first and second year of commercialization. Endo will be responsible for funding and conducting any post-marketing studies and for selling and marketing expenses. The agreement expires with respect to each product upon the later of the expiry of all relevant patents and the 15th anniversary of the date of first commercialization. The agreement may be terminated in various cases, including by Endo in the event the Company experiences delays in obtaining regulatory approval for the products or fails to achieve the target labeling and, without cause, upon sixty days' notice, provided that, in such an event, Endo shall pay an undisclosed termination fee to the Company.

In April 2004, the Company entered into a strategic marketing agreement with Medeus for the marketing and distribution of DepoDur in Europe. The Company will receive a share of sales of DepoDur that will increase from an initial 35% to a maximum of 50% of net sales as certain sales thresholds are reached. The Company will also receive a payment on signing and will receive further future milestone payments on attainment of marketing approvals, commercial launches and sales targets; if all targets are met these payments will amount to over €100 million. The Company will be responsible for the cost of manufacturing the product and clinical development required to gain and maintain approvals throughout the expanded EU. Medeus will be responsible for the cost of all sales and marketing of the product, including pre-launch development and any further clinical studies (other than Phase IV studies for market development, for which the parties will collaborate).

In June 2002, the Company signed a Joint Agreement with GeneMedix to develop an extended release formulation of interferon alpha-2b using the Company's DepoFoam technology. Prior to entering into this agreement, the Company had already formulated interferon alpha-2b with its DepoFoam technology. Reflecting this, and the value of DepoFoam licensing rights, SkyePharma received from GeneMedix non-refundable consideration of £3.25 million. The consideration was in the form of an unsecured Convertible Loan Note, issued by GeneMedix, carrying a 5% coupon, which is convertible at any time into between approximately 8.3 million and 11.2 million fully paid, ordinary GeneMedix shares. GeneMedix has the option to redeem the Note for cash in certain circumstances. In addition, SkyePharma will receive undisclosed milestones payable against progress through clinical development. The two companies will assume equal shares of further development and manufacturing costs and will also share potential milestones and royalties received from a third party on the eventual out-licensing and sales of the product. Following initial studies, the Company and GeneMedix are discussing the future of this collaboration.

***Inhalation***

In November 1998, the Company and Novartis agreed to jointly develop a new formulation of Novartis' Foradil® asthma drug using the Company's multi-dose dry powder inhaler. The Company is responsible for producing the drug in its finished form, including supplying both the powder and the device as a product to Novartis. Under the arrangement, Novartis has paid the Company a technology access fee of £0.4 million and made an equity investment in the Company amounting to £6.1 million. Novartis has also agreed to pay the Company royalty income on future worldwide sales of the drug. In return, the Company has granted Novartis an exclusive worldwide license to market Foradil® in the new delivery form.

In December 2001, the Company signed exclusive agreements with AstraZeneca PLC to develop the next generation of AstraZeneca's Pulmicort® MDI. The Company will apply one of its inhalation delivery technologies using HFA as propellant to replace CFC's in the currently marketed MDIs. Under the terms of the agreement, the Company will be responsible for all pre-clinical and clinical development, as well as compiling regulatory filings for marketing approval. The Company received a signing fee of \$2 million and progress related payments could total up to \$10 million once marketing approval is granted. AstraZeneca has also agreed to pay the Company royalty income on future net sales of the HFA-based product. The Company has already developed an internal formulation of budesonide, the active ingredient in Pulmicort® that is pharmaceutically stable and suitable for use in an HFA-MDI. Phase II clinical studies on the AstraZeneca formulation have been completed and Phase III clinical studies commenced in June 2003.

***Topical***

As set out above under "Drug Delivery Platforms Topical Approved Topical Products Solaraze®", the Company entered into two agreements with Bioglan: for the manufacture, marketing and distribution of Solaraze® in Europe and for the license of marketing rights to the United States, Canada and Mexico. As set out above, during 2001, SkyePharma agreed the transfer of rights to market Solaraze® in the United States, Canada and Mexico from Bioglan to Quintiles. On May 13, 2002, following negotiations with the Administrators of Bioglan, SkyePharma announced an agreement to transfer all rights to market Solaraze® in Europe to Shire for a total consideration up to £15 million, plus royalties on European sales. Of this total consideration, £2.1 million is contingent on conditions including Solaraze®'s launch in certain European countries.

On April 29, 2004 the Company announced that it had licensed the rights to its dermatology assets, which account for substantially all of its topical drug delivery technologies, for those territories that are not covered by existing licenses, to Trigenesis. The rights relate to three marketed drugs, including Solaraze®, rights to six pipeline products, including Hyclinda and Acyclovir, and six proprietary and complementary delivery technologies, including HA-based technologies, Crystalip, Dermastick, ES-Gel, Dissocubes and Solid Lipid Nanoparticles. Under the agreement, Trigenesis is obligated to exploit the dermatology assets covered by the license and to continue the development of those drug candidates that are currently at the pipeline stage. Trigenesis has also assumed the majority of SkyePharma's existing obligations to third parties with respect to the development of these drug candidates. All rights granted by the Company to licensees under existing licenses remain unaffected by the agreement. In addition, the Company has retained the right to use the technologies subject to the license for the development of a number of new chemical entities in the dermatology area and, in certain cases, also for non-dermal applications.

The Company received a payment on signing and for each of the six pipeline products may receive additional milestones on completion of Phase III trials and on approval. If all six products reach the market in the United States and Europe, total milestone payments (including the payment on signing) will be in excess of US\$20 million. The Company will also receive a 10% royalty on sales of these products by Trigenesis and 35% of any sub-license income. Trigenesis will be obligated to develop the pipeline products and to exploit the delivery technologies and will also

assume certain of the Company's existing obligations to third parties involved in development. Trigenesis will be obligated to develop the pipeline products and to exploit the delivery technologies and will also assume certain of the Company's existing obligations to third parties involved in development.

Subsequent to the completion of the Trigenesis agreement, Trigenesis announced on May 6, 2004, that it was being acquired by Dr Reddy's, an Indian pharmaceutical company, which will assume all the obligations of Trigenesis.

#### ***Solubilization***

In December 2002, the Company entered into a development and commercialization agreement under which Endo received an exclusive license to the U.S. and Canadian marketing and distribution rights for two of the Company's patented development products, DepoDur<sup>®</sup>, an injectable product, and Propofol IDD-D<sup>®</sup>, with options to negotiate for other development products in the area of pain management. For a discussion of the terms of this agreement, see "Collaborative Arrangements - Injectable".

SkyePharma Canada and Jagotec AG have signed an exclusive agreement with Baxter Healthcare Corporation to collaborate on the use of the IDD and nano-particulate technology for the formulation of injectable medications. Details of this collaboration are set out above under "Drug Delivery Platforms - Solubilization - Solubilization Products in Development - New Product Feasibility Programs".

#### ***Other Collaborative Arrangements***

In December 2000, SkyePharma entered into an agreement with Paul Capital. Under the agreement, Paul Capital provided a total of \$30 million between 2000 and 2002, in return for the sale of a portion of potential future royalty and revenue streams from DepoDur<sup>®</sup>, Xatral<sup>®</sup> OD, Solaraze<sup>®</sup> and DepoCyt<sup>®</sup>. The monies will be used to fund the clinical development of DepoDur<sup>®</sup>. Between January 2003 and December 2014, Paul Capital will receive 15% of the annual royalties and revenues from the stated products up to an agreed ceiling. Once the predetermined ceiling is reached, the percentage participation will fall to 3% for the remainder of the period until December 31, 2014.

In March 2002, SkyePharma entered into a second agreement with Paul Capital. Under the terms of the agreement, Paul Capital paid SkyePharma \$30 million during 2002 and 2003, in return for a portion of the future royalty and revenue streams from nine products from the Company's pipeline. The monies will be used principally to fund the clinical development of Propofol IDD-D<sup>®</sup> and HFA-formoterol. The nine products referred to are Propofol IDD-D<sup>®</sup> and HFA-formoterol, the lipid-lowering drug fenofibrate, an anti-cancer agent busulfan, an intravenous formulation of the antibiotic oxytetracycline, oral budesonide to treat inflammatory bowel disease, HFA-budesonide and Foradil<sup>®</sup>, for the treatment of asthma, and the anti-depressant Paxil CR<sup>®</sup>. Between January 2002 and December 2015, Paul Capital will receive between 4% and 20% of the annual royalties and revenues from the total of nine products. The 20% rate applies first. The percentage then falls, when an agreed return is achieved, to 12.5% until a second ceiling is reached, before falling to 4% for the remainder of the period until December 31, 2015. During 2002 and 2003, the 20% rate will be reduced based on the percentage of the total \$30 million already funded. In addition, should the share of royalties received by Paul Capital not meet minimum returns, SkyePharma may issue SkyePharma ordinary shares up to a value of \$7.5 million. The number of ordinary shares to be issued is capped based upon a minimum price of 55 pence per share. Also under the terms of these agreements, Paul Capital has been issued warrants carrying rights to subscribe for 5 million SkyePharma ordinary shares at an exercise price of 73.75 pence, representing a 25% premium to the average trading price for the five trading days immediately prior to the closing date.

In December 2001, the Company entered into several agreements concerning the development of Astralis' novel injectable vaccine therapy, for the treatment of all forms of psoriasis, a chronic skin disorder. A first generation of Psoraxine, developed by Astralis, has completed clinical studies in Venezuela with encouraging results. Under the terms of a technology access agreement, the Company received from Astralis a \$5 million license fee, for access to DepoFoam and other relevant drug delivery technologies. In addition, through a service agreement, the Company will provide all development, manufacturing, pre-clinical and clinical development services to Astralis for second generation Psoraxine, up to the completion of Phase II clinical studies. In the event that Phase II studies are successfully completed, Astralis will offer SkyePharma the option to acquire the worldwide licensing and distribution rights to Psoraxine. If SkyePharma does not exercise the option, Astralis will seek a marketing partner to fund Phase III clinical studies and to provide a sales and marketing infrastructure. In September 2003 Astralis initiated a Phase I clinical trial in the United States. This trial was successfully completed and in March 2004 Astralis announced that it had initiated a Phase II clinical trial in the United States.

In a separate transaction, the Company made a total equity investment in Astralis of \$20 million in convertible preferred shares. In January 2004 SkyePharma converted all of its convertible preferred shares into 25 million common shares, 12.5 million of these being in escrow. The resulting holding represents approximately 35.7% of the common shares of Astralis.

On May 14, 2002, SkyePharma announced its intention to enter a wide ranging strategic collaboration with Kowa Company Ltd., a leading Japanese company with substantial pharmaceutical interests. Kowa and SkyePharma also signed a separate non-binding Letter of Intent to evaluate Kowa's acquisition of a 50% interest in SkyePharma's manufacturing facility in Lyon. Kowa and the Company are still evaluating the proposal although no significant activity took place in the last year in respect of this. On June 25, 2002, the Company announced that in accordance with the terms of an agreement dated May 13, 2002, and following shareholder approval at an Extraordinary General Meeting of the Company held on June 7, 2002, thirty million ordinary shares of 10p each in SkyePharma PLC had been allotted to Kowa Company Limited, for a total consideration of £25,320,000. This represented a holding of 5.01% after the investment. As part of its investment, Kowa had the right to appoint a non-executive director to the board of SkyePharma and on October 30, 2002, the Company confirmed the appointment of Mr. Torao Yamamoto as a Non-executive Director of SkyePharma. Kowa and SkyePharma have an active relationship involving the formulation, development scale-up and manufacturing for clinical trials for a number of products in Kowa's development pipeline including a new lipid lowering agent, NK-104.

In January 2003, the Company and Enzon Pharmaceuticals, Inc. agreed a strategic alliance based on a broad technology access agreement. The two companies will draw on their combined drug delivery technology and expertise to jointly develop up to three products for future commercialization. These products will be based on the Company's proprietary platforms in the areas of oral, injectable and topical drug delivery, supported by technology to enhance drug solubility and Enzon's proprietary PEG modification technology, for which Enzon received a US\$3.5 million technology access fee. The Company will receive a milestone payment for each product based on its own proprietary technology that enters Phase II clinical development. Research and development costs related to the technology alliance will be shared equally, as will future revenues generated from the commercialization of any jointly-developed products. Whilst a number of compounds have been evaluated, there are currently no products in active development under this technology alliance. PEG technology involves the attachment of polyethylene glycol to therapeutic proteins or small molecules, for the purpose of enhancing therapeutic value. Polyethylene glycol is a relatively non-reactive and non-toxic polymer that is frequently used in food and pharmaceutical products. The attachment of polyethylene glycol to a molecule increases its molecular weight, and for some proteins and small molecules can impart better solubility and stability, reduce immune responses, improve therapeutic and/or safety profiles and simplify or improve dosing regimens.



On May 17, 2004 the Company announced an exclusive agreement with First Horizon Pharmaceutical Corporation ("First Horizon") through which the Company granted First Horizon the exclusive U.S. marketing and distribution rights for an undisclosed cardiovascular product. This product is currently under review by the FDA for approval, which is expected by the end of 2004. In addition, First Horizon also obtained the right of first refusal to negotiate a license to develop and commercialize a future cardiovascular product utilizing the Company's delivery technology.

The Company will receive a total of up to \$50 million in milestone payments and 25% of First Horizon's net sales of the product. \$5 million was paid to the Company upon signing the Agreement and up to an additional \$15 million is payable thereafter, all of which are contingent upon milestones related to FDA approval. In addition to the \$20 million in payments, the Company will receive up to \$30 million in sales based milestone payments. The Company will manufacture and supply the product from its Lyon manufacturing facility. The Company will also make a contribution of up to \$5 million to First Horizon's initial marketing expenses to establish the product.

### **Patents and Proprietary Rights**

The Company believes that patent and other intellectual property protection of its drug delivery and formulation technologies is important to its business and that its future performance will depend in part on its ability to obtain patents, maintain confidential and trade secret information and to operate without infringing the intellectual property rights of others.

#### ***Oral Controlled Release Technology***

The Company has two patent families in respect of its core Geomatrix technologies.

The first patent family was issued in Australia, New Zealand, Italy, Europe, Japan, the United States and Canada. It expired in 2002 in Australia and New Zealand and will expire in 2005 in Italy, 2006 in the rest of Europe, Japan and the United States, and 2009 in Canada. The second patent family relating to the Company's Geomatrix technologies was granted in Italy, the United States and Europe, Canada and Japan. These patents expire between 2009 and 2012.

In addition to the two patent families in respect of its core Geomatrix technologies, the Company has several other granted patents related to its oral controlled release technology, as well as applications filed in markets including Europe, the United States, Japan, Canada, Australia and New Zealand, which continue to protect the technology to 2015. These patents and applications cover a variety of different tablet formulations containing an active drug core and various surface coatings covering the core. These cores and coatings contain excipients that enable a variety of release profiles to be achieved. Later applications cover recent innovations and/or improvements to the original inventions.

In total, the Company has 149 patents protecting the Geomatrix technology, which represents 21 patent families. The Company continues to file additional patent applications relating to oral drug delivery technologies in order to secure protection for its activities in this area.

#### ***DepoFoam Technology***

The Company owns a large portfolio of patents relating to the DepoFoam delivery technology in major jurisdictions. The majority of these patents will continue in force until 2014. Additional filings of patent applications have been made for improvements of the initial technology and for innovative technology relating to this subject matter in major jurisdictions.

In addition, through a prior agreement entered into by SkyePharma Inc. with RDF, RDF granted certain rights, on an exclusive basis, relating to the DepoFoam technology to SkyePharma Inc. Under the agreement, SkyePharma Inc. is obliged to prosecute certain patent applications and maintain issued patents relating to the licensed intellectual property. RDF retains the right to terminate the agreement or to convert the exclusive nature of the rights granted under the agreement into a non-exclusive license in the event that SkyePharma Inc. does not satisfy its

contractual obligations, including making certain minimum annual payments. Additional termination events include bankruptcy and a material breach of the agreement which is not remedied within a specified period. The termination of this agreement or the conversion to a non-exclusive agreement would have a material adverse effect on the Company. In April 2004 the Company entered into an amendment agreement with RDF pursuant to which certain commercial terms of the RDF agreement were re-negotiated. As part of the re-negotiation of these terms, 3.25 million ordinary shares of the Company were issued to RDF.

### ***Inhalation Technology***

The Company has twelve patent families in respect of its inhalation technology. One family covers SkyeHaler itself as well as several of the structural elements and features incorporated therein, and has been granted in major jurisdictions, Switzerland, Europe, the United States, Australia, Canada, Japan and New Zealand and the first to expire of these patents, expires in 2015. Other patent families relate to a dry powder, for use with the Dry Powder Inhalers.

The Company has, together with other companies working in the same area, been involved in several European patent oppositions related to the use of environmentally friendly HFA as propellants. Of these oppositions, four have been settled and the remaining four are in various stages within the European Patent Office. There are currently six oppositions in which SkyePharma is participating in relation to various aspects of inhalation technologies.

On June 2, 2004 the Company announced an alliance with Vectura Limited, which among other things, will give the Company access to Vectura's Aspirair® device and related patents.

### ***Topical Technology***

The Company owns a wide range of intellectual property rights covering its topical technology. Patents and applications covering many and varied uses of hyaluronic acid have been filed throughout the world. Following these filings, patents have been granted in major jurisdictions expiring between 2010 and 2013.

On April 29, 2004, the Company announced that it had licensed the bulk of its topical technology to Trigenesis. For further information see "Business Operations Overview Topical".

### ***Solubilization***

The Company owns two patent families relating to its solubilization technology. The first family relates to solid lipid nanoparticles and the second relates to nano-suspensions, each of which are useful for drug delivery. These patent families, as well as applications filed, protect the Company's technologies in the area of solid lipid nanoparticles and nano-suspensions in major jurisdictions until 2015. The Company also has an exclusive license under two further patent families: one relating to solid polymer nano-particulate technology and the other to further developments in the areas of solid lipid nano-particles and nano-suspensions.

In addition, the Company owns a large portfolio of patents and patent applications covering three broad patent families relating to:

- i) Lipid stabilized microparticle technology (where the drug is a solid particle);
- ii) Lipid stabilized microdroplet technology (where the drug is a liquid); and
- iii) Omega-3 oil stabilized drug technology, which is useful for drug delivery.

This technology is protected by numerous patent and patent application worldwide: 15 U.S. patents and by 70 corresponding patents in countries outside the United States. In addition, the portfolio contains many pending applications, including 23 patent applications in the United States, 35 outside of the United States and in addition 23 regional (European and PCT) patent applications.

### ***Patent Protection***

There can be no assurance that the Company will be issued any additional patents or that, if any patents are issued, they will provide the Company with significant protection or will not be challenged by third parties asserting claims against the Company concerning its existing products or with respect to future products under development by the Company. The Company, from time to time, may receive notification of alleged infringements. The Company may not, in all cases, be able to resolve any such allegations through licensing arrangements, settlement or otherwise. Furthermore, the Company anticipates that any attempt to enforce its patents would be time-consuming and costly. Moreover, the laws of some foreign countries do not protect the Company's proprietary rights in the products to the same extent as does the law of the United States.

There can be no assurance that the Company's patents or any future patents will prevent other companies from developing similar or functionally equivalent products. Furthermore, there can be no assurance that (1) any of the Company's future processes or products will be patentable, (2) any pending or additional patents will be issued in any or all appropriate jurisdictions, (3) the Company's processes or products will not infringe upon the proprietary rights of third parties, or (4) the Company will have the resources necessary to protect its patent rights against third parties. The inability of the Company to protect its patent and proprietary rights or the infringement by the Company of the patent or proprietary rights of others could have a material adverse effect on the Company's business, financial condition or results of operations.

The Company also relies on trade secrets and proprietary know-how which it seeks to protect, in some cases through confidentiality clauses in agreements with its employees and consultants. There can be no assurance that these agreements will not be breached, that the Company would have adequate remedies from any such breach or that the Company's trade secrets will not otherwise become known or be independently developed by competitors.

There has been substantial litigation in the pharmaceutical, biomedical and biotechnology industries with respect to the manufacture, use and sale of new products that are the subject of conflicting patent rights. Most of the brand name controlled-release products of which the Company is developing generic versions are covered by one or more patents. Under the Hatch-Waxman amendments, when a drug developer files an ANDA for a generic drug, and the developer believes that an unexpired patent, which has been listed with the FDA as covering that brand name product, will not be infringed by the developer's product or is invalid or unenforceable, the developer must so certify to the FDA. That certification must also be provided to the patent holder, who may challenge the developer's certification of non-infringement, invalidity or unenforceability by filing a suit for patent infringement. If a suit is filed within 45 days of the patent holder's receipt of such certification, the FDA can review and approve the ANDA, but is precluded from granting final marketing approval of the product until a final judgment in the action has been rendered or 30 months from the date the certification was received, whichever is sooner. Should a patent holder commence a lawsuit with respect to alleged patent infringement by the Company, the uncertainties inherent in patent litigation make the outcome of such litigation difficult to predict. The Company evaluates the probability of patent infringement litigation with respect to its ANDA submissions on a case-by-case basis. The delay in obtaining FDA approval to market the Company's product candidates as a result of litigation, as well as the expense of such litigation, whether or not the Company is successful, could have a material adverse effect on the Company's business, financial condition or results of operations.

### **Manufacturing**

#### ***Manufacturing in Europe***

Manufacturing operations in Europe take place at the Company's Lyon facility in France and Muttenz facility in Switzerland. In Lyon the Company has an approximately 17,000 square meter (183,000 square feet) pharmaceutical manufacturing and production facility and an approximately

2,400 square meter (25,850 square feet) adjoining office complex. In Muttentz the Company has a 9,647 square meter (103,826 square feet) facility. The Company presently manufactures four Geomatrix products: Madopar DR® in its Muttentz facility and Diclofenac-ratiopharm-uno, Xatral® OD and Coruno® in its Lyon facility. The Company produces bio-batches for its internal development products and its collaborative partners in both facilities.

The Lyon facility was designed and built for drug production in 1993 by American Cyanamid but was used instead for packaging activities. Under the terms of the Company's 1997 acquisition of the facility from AHP, the Company's manufacturing activities were gradually transferred into the facility and the Company also packaged certain pharmaceutical products and other products ("Contract Products") on behalf of certain subsidiaries of AHP. The facility is in compliance with cGMP with respect to packaging operations and it has European regulatory approval to package the Contract Products.

The Company has completed its Geomatrix manufacturing suite in the Lyon facility at a capital cost of approximately £7.1 million. This facility is used to manufacture products for collaborative partners and for the Company. The facility enables the Company to manufacture its own products in addition to contracting with third parties. Currently, manufacturing operations for Xatral® OD, Coruno® and Diclofenac-ratiopharm-uno take place at the Company's Lyon facility. The Company has brought the facility into compliance with cGMP and FDA standards at a cost of approximately £0.8 million. The FDA has inspected the Lyon facility in respect of four products: Dilacor® XR, Coruno®, Xatral® OD and an undisclosed oral product. All these pre-approval inspections have been passed without critical deficiency in cGMP being noted. In July 2001, the FDA approved the Lyon facility for the commercial manufacturing of one of these products, Dilacor® XR. Manufacturing of Coruno® started in April 2003 and Xatral® OD in March 2004. The plant has also been inspected for manufacturing of an undisclosed oral product. There can be no assurance, however, that the Lyon facility will ultimately be found to be in compliance with cGMP or other regulatory requirements for the purposes for which the Company plans to use the facility. Failure to comply could result in significant delays in the Company's planned manufacturing efforts. The Company also could incur significant additional expense in bringing the facility into compliance with cGMP or other regulatory requirements. In 2004, the plant has expanded its oral manufacturing facilities to include two large scale microfluidizers for the production of an undisclosed oral product. Scale-up to the final commercial scale is expected to be completed in the second half of 2004.

The Company has expanded its operations at the Lyon facility to include production activities for dry powder inhaler products pursuant to the Novartis development contract, see "Drug Delivery Platforms Inhalation Inhalation Products in Development", at a capital cost to date of approximately £8.1 million. In December 2003, the FDA approved the facility for the commercial filling of the Foradil® Certihaler®, which is expected to begin in 2004. The dry powder inhaler (SkyeHaler) will be manufactured by a Swiss plastic contract manufacturer, Riwisa AG. Finally assembly and filling with the powder blend containing formoterol fumarate will take place in the Lyon facility. The product will be then released for marketing at the Lyon facility and delivered to Novartis for final packaging and distribution.

On May 14, 2002, SkyePharma announced its intention to enter a wide-ranging strategic collaboration with Kowa Company Ltd., a leading Japanese company with substantial pharmaceutical interests. Kowa and SkyePharma signed a separate non-binding Letter of Intent to evaluate Kowa's acquisition of a 50% interest in SkyePharma's manufacturing facility in Lyon. Kowa and the Company are still evaluating this proposal although no significant activity took place in the last year in respect of this. Kowa and SkyePharma have an active relationship involving the formulation, development scale-up and manufacturing for clinical trials for a number of products in Kowa's development pipeline including a new lipid lowering agent, NK-104. For additional information, see "Item 7: Major Shareholders and Related Party Transactions Major Shareholders".

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

Due to EMEA requirements to retest drugs being imported into Europe, retesting and packaging operations were established at the Lyon facility during 2003 and 2004 for DepoCyt® supplies for Europe under the Mundipharma marketing and distribution agreement.

### *Manufacturing in North America*

DepoFoam manufacturing operations take place at the Company's facilities in San Diego, California. The Company currently manufactures two DepoFoam products at its facilities for commercial sale, DepoCyt®, and DepoDur .

Manufacturing for DepoCyt® takes place in an approximately 2,020 square meter (21,746 square feet) facility built for this purpose. This facility complies with cGMP regulations and has been licensed for drug manufacturing by the State of California. The facility is approved for the manufacture of DepoCyt® by the FDA and EMEA.

Commercial manufacturing for DepoDur will take place in an approximately 7,600 square meter (82,000 square feet) facility housing, production, administrative and research and development activities. This facility complies with cGMP regulations and the Company has been informed that the FDA has granted approval for such commercial manufacturing. Clinical trial materials are also manufactured in this facility. Prior to marketing any drugs (including DepoCyt® and DepoDur ) outside countries where approval has been gained, the Company will need to meet applicable regulatory standards, achieve prescribed product quality and reach necessary levels of production of such products in order to obtain marketing approvals in such countries.

To date, SkyePharma Inc. has relied on a particular method of manufacture for products based on its DepoFoam technology which involves processes known only to SkyePharma Inc. There can be no assurance that this method will be applicable to all pharmaceuticals the Company desires to commercialize. Further, the yield of DepoFoam product may be highly variable for different drugs. Finally, the Company will need to successfully meet any manufacturing challenges associated with the characteristics of the drug to be encapsulated. The physical and chemical stability of the DepoFoam formulation may vary with each drug over time and under various storage conditions. There can be no assurance that the manufacturing process will result in economically viable yields of product or that it will produce formulations of therapeutic products sufficiently stable under suitable storage conditions to be commercially useful.

In the event that the Company decides to pursue alternative manufacturing methods for some or all of its injectable drugs utilizing DepoFoam , there can be no assurance that these methods will prove to be commercially practical or that the Company will have or be able to acquire rights to use such alternative methods.

In connection with its collaborative arrangements, the Company may elect to maintain exclusive formulation and manufacturing rights to any DepoFoam encapsulated drugs, or enter into a technology transfer agreement with corporate partners, which would allow such corporate partners to manufacture a DepoFoam formulation of the partner's drug under license from SkyePharma. Under these arrangements, the Company would receive compensation based on the manufacturing costs of the product or royalties, or both.

### *Manufacturing Partners*

While the Company has its own manufacturing sites for Geomatrix , inhalation and DepoFoam manufacturing, for the manufacture of certain of its existing products, and certain of those currently in development, the Company will depend on manufacturing partners.

Under the terms of the development and commercialization agreement with Endo for DepoDur and Propofol IDD-D signed in December 2002, in respect of the United States and Canada, the Company is primarily responsible for the clinical development of the products up to final FDA approval and for product manufacture, including all associated costs. Upon approval, Endo will market each product in the United States and Canada with the Company as supplier. The

Company currently has no internal manufacturing site equipped to manufacture its IDD solubilization products and therefore in 2003 entered into a supply agreement with a manufacturing partner for Propofol IDD-D for these territories. The Company has also agreed to qualify and obtain final regulatory approval for a second manufacturing site for DepoDur and Propofol IDD-D, either internally or through a third party manufacturing partner, within a specified period from the date of first commercial sale.

### **Supplies and Raw Materials**

The Company and its collaborative pharmaceutical company partners rely on certain suppliers of key raw materials. Certain of those materials are purchased from single sources and others may be purchased from single sources in the future. Although the Company has no reason to believe that it and its collaborative pharmaceutical company partners will be unable to procure adequate supplies of such raw materials on a timely basis, and at commercially reasonable rates, disruptions in supplies, including delays due to the inability of the Company's pharmaceutical company partners, the Company or its manufacturers to procure raw materials, would have a material adverse effect on the Company's business.

Regulatory requirements for pharmaceutical products tend to make the substitution of suppliers costly and time-consuming. The inability to develop alternative sources could have a material adverse effect on the Company's ability to manufacture and market its products.

One of the DepoFoam Injectable products DepoDur, has morphine sulphate as its active ingredient. Morphine sulphate is classified as a Scheduled Drug by the United States Drug Enforcement Agency ("DEA"). The DEA has determined that these drugs have a high potential for abuse and could lead to severe psychological or physical dependence. The DEA controls the national production and distribution of certain Scheduled Drugs in the United States by allocating production quotas based, in part, upon the DEA's view of national demand. SkyePharma Inc. has a DEA license to use morphine sulphate in its research and manufacturing of DepoDur. While the Company expects that adequate quantities of the drug will be available to it to meet future research and commercial requirements, there can be no assurance to that effect.

### **Sales and Marketing**

At present, the Company is not involved in the consumer marketing of products formulated with its technologies. The Company depends on its collaborative partners for such marketing. The majority of the Company's partners are not obligated to market products incorporating its technologies, even if such products are successfully developed and approved. However, in some more recent collaborations, contracts have included certain commitments for the Company's partners to market products developed in collaboration with the Company.

### **Competition**

The pharmaceutical industry is highly competitive and is affected by new technologies, governmental regulations, health care legislation, availability of financing and other factors. Many of the Company's competitors have longer operating histories and greater financial, marketing and other resources than the Company.

The Company is and will continue to be subject to competition from numerous other entities that currently operate, or intend to operate, in the pharmaceutical industry. These include companies that are engaged in the development of controlled-release technologies and products, as well as other pharmaceutical manufacturers that may decide to undertake in-house development of these products.

As the pharmaceutical industry continues to consolidate and as pressures increase for cost-effective research and development, some pharmaceutical companies have reduced and may continue to reduce their funding of research and development. Competition for limited client

financing may therefore increase, and this competition could include the clients' internal research and development programs, other drug delivery programs and other technologies and products of third parties.

### **Government Regulation**

All drugs and medical devices, including the Company's products under development, are subject to extensive regulation in the United States and Europe, the Company's two principal markets. In the United States, the primary regulatory body is the FDA, although to a lesser extent state and local authorities are also involved in the regulatory process. In Europe, there are two regulatory systems. There is a European Union system that is the responsibility of the EMEA. In addition, each country has its own regulatory agency. In both the United States and Europe, the applicable regulations govern or influence the development, testing, manufacture, safety, labeling, storage, record keeping, approval, advertising, promotion, sale and distribution of prescription pharmaceutical products. Pharmaceutical manufacturers are also subject to certain record keeping and reporting requirements, establishment registration and product listing and agency inspections. In addition, acts of foreign governments may affect the price or availability of raw materials needed for the development or manufacture of generic drugs.

#### *United States*

The federal Food, Drug and Cosmetics Act ("FDCA"), the Public Health Services Act, the Controlled Substances Act and other federal statutes and regulations govern or influence all aspects of the Company's business. Noncompliance with applicable requirements can result in fines and other judicially imposed sanctions, including product seizures, injunctive actions and criminal prosecutions. In addition, administrative or judicial actions can result in the recall of products, and the total or partial suspension of the manufacturing of products, as well as the refusal of the government to approve pending applications or supplements to approved applications. The FDA also has the authority to withdraw approvals of drugs in accordance with statutory due process procedures.

FDA approval is required before any dosage form of any new unapproved drug, including a generic equivalent of a previously approved drug, can be marketed. All applications for FDA approval must contain information relating to evidence of safety and efficacy or bio-equivalence to a listed reference drug, product formulation, stability, manufacturing processes, packaging, labeling and quality control.

#### *ANDA Process*

The Drug Price Competition and Patent Restoration Act of 1984, known as the Hatch-Waxman Act, established abbreviated application procedures for obtaining FDA approval for those drugs which are off-patent and whose non-patent exclusivity under the Hatch-Waxman Act has expired and which are shown to be bioequivalent to brand-name drugs. Approval to manufacture these drugs is obtained by filing an ANDA. An ANDA is a comprehensive submission which generally must contain data and information pertaining to the bioequivalence of the drug covered by the ANDA to a referenced listed drug, formulation specifications, stability data, analytical data, methods and manufacturing validation data and quality control procedures. As a substitute for clinical studies, the FDA requires data indicating that the ANDA drug formulation is bioequivalent to a previously approved NDA drug. In order to obtain an ANDA approval of a strength or dosage form which differs from the referenced brand-name drug, an applicant must file and have granted an ANDA Suitability Petition. A product is not eligible for ANDA approval if it is not bioequivalent to the referenced brand-drug or if it is intended for a different use. However, such a product might be approved under a Section 505(b)(1) or (b)(2) NDA with supportive data from clinical trials.

The advantage of the ANDA approval process is that an ANDA applicant generally can rely upon bioequivalent data in lieu of conducting pre-clinical testing and clinical trials to demonstrate

that a product is safe and effective for its intended use(s). While the FDCA provides for a 180-day review period, the Company believes the average length of time between initial submission of an ANDA and receiving FDA approval is at least two years.

While the Hatch-Waxman Act established the ANDA, it has also fostered pharmaceutical innovation through such incentives as market exclusivity and patent restoration. The Hatch-Waxman Act provides two distinct market exclusivity provisions which either preclude the submission or delay the approval of a competitive drug application. A five-year marketing exclusivity period is provided for new chemical compounds and a three-year marketing exclusivity period is provided for applications containing new clinical investigations essential to the approval of the application. The non-patent marketing exclusivity provisions apply equally to patented and non-patented drug products. Any entitlement to patent marketing exclusivity under the Hatch-Waxman Act is based upon the term of the original patent plus any patent extension granted under the Hatch-Waxman Act as compensation for reduction of the effective life of a patent as a result of time spent by the FDA in reviewing the innovator's NDA. The patent and non-patent marketing exclusivity provisions do not prevent the filing or the approval of a full Section 505(b)(1) NDA. Additionally, the Hatch-Waxman Act provides 180-day marketing exclusivity against effective approval of another ANDA for the first ANDA applicant who submits a certification challenging a listed patent as being invalid or not infringed and successfully defends in court any patent infringement action based on such certification.

#### *NDA Process*

An NDA is a filing submitted to the FDA to obtain approval of a new drug or a new formulation of an existing drug and must contain complete pre-clinical and clinical safety and efficacy data or a right of reference to such data. Before dosing a new drug in healthy human subjects or patients may begin, stringent government requirements for pre-clinical data must be satisfied. The preclinical data, typically obtained from studies in animal species, as well as from laboratory studies, are submitted in an Investigational New Drug application, or its equivalent in countries outside the United States where the relevant clinical trials are to be conducted. The pre-clinical data must provide an adequate basis for evaluating both the safety and the scientific rationale for the initiation of clinical trials.

Clinical trials are typically conducted in three phases: Phase I, II and III. A description of each of these phases of development is included in "Research and Development Development Process for Brand-Name Pharmaceuticals". Data from pre-clinical testing and clinical trials are submitted to the FDA as an NDA for marketing approval. The process of completing clinical trials for a new drug is likely to take several years and require the expenditure of substantial resources. Preparing an NDA or marketing authorization application involves considerable data collection, verification, analysis and expense, and there can be no assurance that approval from the FDA will be granted on a timely basis, if at all. The approval process is affected by a number of factors, primarily the risks and benefits demonstrated in clinical trials as well as the severity of the disease and the availability of alternative treatments. The FDA may deny an NDA or marketing authorization application if the regulatory criteria are not satisfied, or such authorities may require additional testing or information.

Even after initial FDA approval has been obtained, further studies, including Phase IV post-marketing studies, may be required to provide additional data on safety and will be required to obtain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested. Also, the FDA or other regulatory authorities require post-marketing reporting to monitor the adverse effects of the drug. Results of post-marketing programs may limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process or labeling or a change in manufacturing facility, an application seeking approval of such changes must be submitted to the FDA or other regulatory authority. Additionally, the FDA regulates post-approval promotional labeling and advertising activities to assure that such activities are being conducted in



conformity with statutory and regulatory requirements. Failure to adhere to such requirements can result in regulatory actions which could have a material adverse effect on the Company's business, results of operations and financial condition.

The FDCA provides for NDA submissions that may rely in whole or in part on publicly available clinical data on safety and efficacy under section 505(b)(2) of the FDCA. The Company and its collaborative partners may be able to rely on existing publicly available safety and efficacy data in filing NDAs for extended-release products when such data exist for an approved immediate-release version of the same chemical entity. However, there is no guarantee that the FDA will accept such applications under section 505(b)(2), or that such existing data will be publicly available or useful. Further, utilizing the section 505(b)(2) application process is uncertain, because neither the Company nor the FDA have had significant experience with it. Additionally, under the Prescription Drug User Fee Act of 1992 (the "PDUFA"), all NDAs require the payment of a substantial fee upon filing, and other fees must be paid annually after approval. Under the PDUFA, there are circumstances when waivers may be granted to the payment of user fees. No assurances exist that, if approval of an NDA is required, such approval can be obtained in a timely manner, if at all.

#### *Other Regulation*

The Prescription Drug Marketing Act ("PDMA"), which amends various sections of the FDCA, imposes requirements and limitations upon drug sampling and prohibits states from licensing wholesale distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include, among other things, state licensing of wholesale distributors of prescription drugs under federal guidelines that include minimum standards for storage, handling and record keeping. In addition, the PDMA sets forth civil and criminal penalties for violations of these and other provisions. Various sections of the PDMA are still being implemented by the FDA and the states. Nevertheless, failure by the Company's distributors to comply with the requirements of the PDMA could have a material adverse effect on the Company's business, results of operations and financial condition.

Manufacturers of marketed drugs must comply with cGMP regulations and other applicable laws and regulations required by the FDA, the Environmental Protection Agency, the DEA, the HPB in Canada, the EMEA in the European Union and other regulatory agencies. Failure to do so could lead to sanctions, which may include an injunction suspending manufacturing, the seizure of drug products and the refusal to approve additional marketing applications. The Company seeks to ensure that any third party with whom it contracts for product manufacturing will comply with cGMP. The FDA conducts periodic inspections to ensure compliance with these rules. However, there can be no assurance that any such third parties will be found to be in compliance with cGMP standards. Any such non-compliance could result in a temporary or permanent interruption in the development and testing of the Company's planned products or in the marketing of approved products, as well as increased costs. Such non-compliance could have a material adverse effect on the Company's business, results of operations and financial condition. In addition, SkyePharma Inc.'s manufacturing facility located in San Diego, California is regulated by the State of California, Department of Health Services, Food and Drug Branch, and the DEA.

#### *European Union Regulation*

The European drug registration system is based on co-operation between the EMEA, established in London, and competent national authorities of the member states of the European Union.

Since 1995, two new registration procedures have been available throughout the European Union.

The first of these is a centralized procedure which is compulsory for medicinal products derived from biotechnology, and available at the request of companies for other innovative new products. Under this procedure Marketing Authorization Applications (MAA's) are submitted to the EMEA in

London. At the conclusion of the EMEA's internal scientific evaluation, the opinion of the EMEA's scientific committee is transmitted to the European Commission, the approval of which will form the basis of a single market authorization applying to the whole European Union.

The second procedure is "mutual recognition" which is mandatory for most conventional medicinal products. It is based upon the principle of mutual recognition of national authorizations and it provides for the extension of an MAA granted by one member state of the European Union to one or more other member states identified by the applicant. Should the original national authorization not be recognized in another member state, the points in dispute are submitted to EMEA's scientific committee for arbitration.

In both cases, the final decision is adopted by the European Commission, with the assistance of the EMEA or, in the event of serious disagreement between the member states, by the European Council. In addition, certain European countries outside the European Union follow the decisions of the European Commission.

In addition to the above forms of regulation, price constraints on pharmaceutical products exist in most countries either through governmental regulation or pressure from healthcare organizations. In some countries, governments or governmental agencies are substantial purchasers of human healthcare products and this also imposes an indirect form of regulation on the industry.

### **Environmental Matters**

The Company's operations are subject to a number of environmental laws and regulations in each of the jurisdictions in which it operates governing, among other things, air emissions, wastewater discharges, the use, handling and disposal of hazardous substances and wastes, soil and groundwater contamination, as well as employee health and safety. Environmental compliance obligations and liability risks are inherent in many of the Company's manufacturing activities.

The Company is committed to protecting the environment in which it conducts its activities. The Company's Environmental Policy aims to foster a positive attitude towards the environment and to raise awareness of employees to responsible environmental practices at all sites operated by the Company. The Company aims to set a high standard through continuous improvement in its environmental performance. In the second half of 2003 the Company introduced a system and now undertakes routine monitoring of various measures of its environmental performance at its main R&D and manufacturing sites in Switzerland, France and the U.S., the results of which are submitted to external review bodies.

The Company believes that its operations are currently in material compliance with all applicable environmental laws and regulations. In many jurisdictions, environmental requirements may be expected to become more stringent in the future, which could affect the Company's ability to obtain or maintain necessary authorizations and approvals and result in increased environmental compliance costs. While the Company's management does not believe that environmental compliance or remedial requirements are likely to have a material effect on the Company, there is no assurance that future material environmental compliance or remedial obligations will not arise in connection with the Company's operations or facilities or that such obligations will not have a material adverse effect on its business, financial condition or results of operations.

**ORGANIZATIONAL STRUCTURE**

SkyePharma PLC is an international pharmaceutical company and has a number of wholly-owned subsidiaries.

Company	Country of incorporation	% Held <sup>(1)</sup>
SkyePharma Canada Inc.*	Canada	100%
SkyePharma Production SAS*	France	100%
Krypton Limited	Gibraltar	100%
SkyePharma Holding AG*	Switzerland	100%
Jago Holding AG	Switzerland	100%
SkyePharma AG	Switzerland	100%
Jagotec AG	Switzerland	100%
SkyePharma Holding Inc.*	U.S.	100%
SkyePharma US Inc.	U.S.	100%
SkyePharma Inc.	U.S.	100%
SkyePharma AB*	Sweden	100%

\*  
Directly held by SkyePharma PLC.

(1)  
Portion of ownership interest equals portion of voting power held.

**Property, Plants and Equipment**

The Company's principal executive offices are located in an approximately 850 square meter (9,150 square feet) facility in London, England. The premises are occupied pursuant to a lease expiring in December 2005 at a total annual rent of approximately £522,000 per year. The Company also leases office space in New York City, New York, which expires August 31, 2011. Annual rental fees will range from \$720,000 to \$943,000 during the period, pursuant to a leasing agreement commencing in August 2003. The rental rate was based on an independent valuation. The Company intends to sub-lease part of the premises and is actively seeking a tenant. Following expiry of the Company's short-term lease on its office in Exton, Pennsylvania in December 2002, the Company's U.S. business development operations were moved to the New York office.

In Lyon, France, the Company occupies a 17,000 square meter (183,000 square feet) pharmaceutical manufacturing and production facility and an approximately 2,400 square meter (25,850 square feet) adjoining office complex.

In addition, the Company owns a 3,435 square meter (36,961 square feet) facility in MuttENZ, Switzerland in which its principal research and development, production, small-scale manufacturing, laboratory and workshop operations are housed. In February 1999, the Company purchased a warehousing and administration facility in MuttENZ, Switzerland, of approximately 6,138 square meters (66,045 square feet), including approximately 2,040 square meters (22,000 square feet) previously occupied by the Company under a leasing agreement. The building has since been extended and refitted to house additional administrative, research and laboratory operations, and the building was officially re-opened on April 7, 2001.

SkyePharma Inc. maintains its principal operations in two leased buildings in San Diego, California. Its principle building is an approximately 7,600 square meter (82,000 square feet) facility housing production, administrative and research and development activities. This facility complies with cGMP regulations and the Company has been informed that the FDA has granted approval for the commercial production of DepoDur at this site. Clinical trial materials are also manufactured in this facility. The future minimum annual rental commitment for this facility will range from \$3.0 million to \$4.3 million per year over the balance of the remaining lease term of approximately 12 years based upon pre-established annual rent increases.

The second building is an approximately 2,020 square meter (21,746 square feet) facility built for the manufacture of DepoCyt®. This facility complies with cGMP regulations and has been licensed for drug manufacturing by the State of California. The facility is approved for the manufacture of DepoCyt® by the FDA and EMEA. The lease on this facility expires in January 2006 and annual rental fees will range from \$686,000 to \$720,000 in this period. The Company is currently renegotiating this lease with the aim of extending the term beyond January 2006.

Additionally, SkyePharma Inc. maintains a third leased facility in San Diego, California, containing primarily office space, with an annual rental cost of \$311,000 to \$327,000 and a lease term expiring in January 2006. The Company is currently renegotiating this lease with the aim of early termination.

SkyePharma Canada maintains its principal operations in a leased 3,340 square meter (36,000 square feet) building located in Montreal, Québec, Canada. The building houses a 1,670 square meter (18,000 square feet) purpose-built facility, including laboratories, approved GMP clean-room, and offices with the remaining 1,670 square meters (18,000 square feet) of space being used for research & development, storage and administrative functions. In August 2003, the Company amended its lease agreement to extend the lease term to expire December 31, 2013. The future minimum rent commitments are Cdn\$ 231,000 per year until December 2013. Concurrently, the Company entered into a sublease with a third party for the facility. The sublease expires December 31, 2013 and provides annual rental income of Cdn\$292,000 to Cdn\$523,000 per annum, over the term of the sublease.

SkyePharma AB maintains its operations in 1,925 square meter (20,720 square feet) leased facilities in Malmö, Sweden. The facility houses research and development and administrative functions. The annual rental commitment for the first term of the rental agreement to November 30, 2003 was SKr 4,930,000. After the first term of the rental agreement SkyePharma AB used the option to prolong the rental agreement for a further 12 months with a 6 month notice period. The annual rental commitment for the period December 1, 2003 to November 30, 2004 is SKr 4,881,000, comprising rental of SKr 3,400,000 and services of SKr 1,481,000. The agreement will not be renewed.

The Company believes that its current facilities are adequate to meet its anticipated needs for the foreseeable future. For further discussion of the Company's manufacturing properties, see "Business Operations Manufacturing" above.

#### **Item 5: Operating and Financial Review and Prospects**

*The following discussion contains forward-looking statements that involve risks and uncertainties. The Company's actual results may differ materially from the results discussed in such forward-looking statements as a result of various factors, including those set forth under the caption "Risk Factors".*

The following discussion and analysis of the financial condition and results of the operations of the Company should be read in conjunction with the Consolidated Financial Statements of the Company, including the related Notes thereto, and the other financial information included in this Annual Report. For the Company's Consolidated Financial Statements as of and for the three years ended December 31, 2003 see the information set forth beginning on page F-1. SkyePharma prepares its consolidated financial statements in accordance with U.K. GAAP, which differ in certain respects from U.S. GAAP. A description of these differences and a reconciliation to U.S. GAAP of the Company's U.K. GAAP retained (loss)/profit for the years ended December 31, 2003, 2002 and 2001 and shareholders' funds at December 31, 2003 and 2002 is set out in Note 32 of the Notes to the Consolidated Financial Statements.

**EXECUTIVE SUMMARY**

SkyePharma's strategy is to be a provider of integrated drug delivery services to the pharmaceutical industry, providing a full range of drug delivery products and services ranging from formulation and development through to commercial manufacturing. As such SkyePharma's operations represent a single business segment, pharmaceuticals, served by a range of drug delivery technologies and services.

The following table indicates the development of the Company's business over the course of the three years ended December 31, 2003 in terms of turnover and profit:

	<b>2001</b>	<b>2002</b>	<b>2003</b>
	(£ in millions)		
Turnover	46.1	69.6	53.2
Operating (loss)/profit	(5.1)	4.7	(39.5)
Retained (loss)/profit	(9.5)	1.1	(43.2)

The Company's turnover principally comprises revenues from three sources:

contract development and licensing, including milestone payments and research and development costs recharged (£29.7 million, 2002: £55.4 million);

royalties receivable from sales by third parties of products developed by the Company (£18.7 million, 2002: £6.8 million); and

manufacturing and distribution related revenue (£4.8 million, 2002: £7.4 million).

The Company is seeking to reduce its current dependence on milestone payments and increase the proportion of its revenues arising from royalties. The amount of milestone payments, if any, that the Company receives in any given period is influenced by a number of unpredictable factors, including scientific developments, the ability of the Company to find suitable partners, the timing of the negotiation and conclusion of agreements with such partners, the timing of regulatory approvals, the market introduction of new products and other factors.

In 2003, turnover decreased by 24% to £53.2 million, compared with £69.6 million in 2002 and the Company incurred an operating loss of £39.5 million and a retained loss of £43.2 million, compared with an operating profit of £4.7 million and a retained profit of £1.1 million in 2002. Under U.S. GAAP, the Company recorded a net loss of £37.1 million, compared with a net loss of £45.3 million in 2002.

The principal reason that the Company experienced a loss after exceptionals of £39.5 million in 2003 is that the Company received less milestone payments than it did in 2002 owing to delays in concluding three key new deals. The exceptional charge of £9.5 million and the reduction in income being recognized under the Paul Capital agreements of £8.1 million also contributed to the 2003 loss.

**CRITICAL ACCOUNTING POLICIES AND ESTIMATES**

The preparation of the Consolidated Financial Statements requires the Company to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. On an on-going basis, the Company evaluates its estimates, including those related to revenue recognition, intangible fixed assets, impairment of fixed assets, deferred consideration and contingent liabilities. The Company bases its estimates on historical experience and on various other assumptions that it considers to be reasonable. Actual results may differ from these estimates under different assumptions or conditions.

## Revenue Recognition

The Company's revenue comprises revenues from contract development and licensing, royalties and manufacturing and distribution.

Contract development and licensing income represents amounts invoiced to customers for services rendered under development and licensing agreements, including milestone payments, technology access fees and research and development costs recharged. Under U.K. GAAP, contract development and licensing income is recognized when earned and non-refundable and to the extent that there are no future obligations pursuant to the revenue, in accordance with the contract terms. Refundable contract revenue is treated as deferred until such time as it is no longer refundable.

Royalty income is typically calculated as a percentage of the net sales achieved by a customer when it sells a product of the Company to the final customer. Advance royalties received are treated as deferred income until earned, when they are recognized as income.

Manufacturing and distribution revenues principally comprise contract manufacturing fees invoiced to third parties and income from product sales.

Under U.S. GAAP, the Company recognizes revenue in accordance with SEC Staff Accounting Bulletin No. 104 (SAB 104). The Company recognizes upfront fees and milestone payments when they are non-refundable and when performance obligations are completed based on the criteria of SAB 104. In situations where those criteria are not met, the Company defers and recognizes upfront non-refundable fees ratably over the performance period. The application of SAB 104 criteria to complex collaboration agreements requires significant estimates and judgment. In addition, in arrangements with multiple deliverables, there may be significant judgment in separating the different revenue generating activities and in determining whether each is a separate earnings process. Milestone payments, if any, related to scientific or technical achievements are recognized as income when the milestone is accomplished. The terms of these arrangements may cause the Company's operating results to vary considerably from period to period. Due to the significant portion of our revenue that we currently receive from upfront fees, milestone payments and certain contract development reimbursements in which recognition criteria differ between U.K. and U.S. GAAP, our results from operations will continue to differ, at times significantly.

The Directors believe that the Group's revenue recognition policy is appropriate, reflecting the appropriateness of recording revenue under U.K. GAAP where costs associated with the revenue have been expensed and the deferral of revenue when it is subject to future obligations on the part of the Company connected with the revenue.

During 2003, the Group released a net £2.1 million of turnover and other operating income under this policy, leaving a total deferral of £15.9 million at the end of 2003 comprising:

### Deferred Income

	At December 31, 2002	Received <sup>(1)</sup>	Recognized <sup>(2)</sup>	At December 31, 2003
		(in £ thousands)		
Contract development and licensing revenue	10,200	26,562	(29,652)	7,110
Other operating income	7,829	7,061	(6,126)	8,764
<b>Total</b>	<b>18,029</b>	<b>33,623</b>	<b>(35,778)</b>	<b>15,874</b>

(1) Amounts "received" comprise amounts received in cash pursuant to the contract terms and amounts included within debtors during 2003. Deferred income at December 31, 2003 will be released under U.K. GAAP in subsequent years as the related costs are incurred or as associated obligations under the relevant contracts are satisfied.

(2) Amounts "recognized" comprise amounts received and not deferred plus amounts released from previously deferred income under U.K. GAAP during 2003.



### **Intangible Fixed Assets**

The Company's intangible fixed assets comprise goodwill, intellectual property and capitalized development costs. The Directors estimate the useful economic life of these assets and the assets are amortized over this period. Future events could cause the Directors to change their view of the estimated economic life of these assets.

Under U.S. GAAP, if appropriate, the Company allocates a portion of the consideration paid to purchase other businesses to acquired in-process research and development with no alternative future use, which is written off directly to net income in the period in which the acquisition is made. The valuation of acquired in-process research and development requires significant management estimates and judgment as to expectations for various products and business strategies. Significant changes to the assumptions and judgments used in the purchase price allocation could result in different valuations for acquired in-process research and development and goodwill.

### **Impairment of Fixed Assets**

The Company reviews the carrying value of fixed assets when there is an indication that the assets may be impaired. First-year impairment reviews are conducted for acquired goodwill and intangible fixed assets. Impairment is determined by reference to the higher of net realisable value and value in use, which is measured by reference to discounted future cash flows. Any provision for impairment is charged to the income statement in the year concerned. Judgments regarding the existence of impairment indicators are based on legal factors, market conditions and operational performance of our acquired businesses. Future events could cause the Company to conclude that impairment indicators exist and that assets may have been impaired. Any resulting impairment loss could have a material adverse impact on the Company's financial condition and results of operations.

Under U.S. GAAP, the Company adopted SFAS No. 142, Goodwill and Other Intangible Assets ("FAS 142") on January 1, 2002. Under FAS 142, goodwill is no longer amortized but will be tested for impairment at least on an annual basis in accordance with the provisions of FAS 142.

The goodwill impairment test involves a comparison of the fair value of our reporting unit as defined under FAS 142, with the carrying amounts of net assets, including goodwill, related to our reporting unit. If the carrying amount exceeds the reporting unit's fair value, the second step of the impairment test involves measuring the amount of the impairment loss, if any. The impairment loss is measured based on the amount by which the implied fair value of goodwill exceeds the carrying amount of goodwill in the reporting unit. Fair values are determined based on valuations that rely primarily on the discounted cash flow method. This method uses future projections of cash flows from the Company's reporting unit and includes, among other estimates, projections of future revenues and expenses, projected capital spending and an assumption of our weighted average cost of capital. If the fair value of the asset determined is less than its carrying amount, a loss is recognized for the difference between the fair value and its carrying value.

Changes in any of these estimates, projections or assumptions could have a material effect on the fair value of any of the Company's fixed assets in future measurement periods and result in an impairment of goodwill with a material effect on the Company's future net income and shareholders' funds under U.S. or U.K. GAAP.

### **Deferred Consideration**

Provisions for deferred consideration payable by the Company comprise the fair value of contingent consideration arising from acquisitions. The eventual outcome is subject to the Group's future performance and certain contractual terms. Provisions are reviewed annually by the Directors, who make significant judgments as to the estimated fair value of the contingent consideration. Based on these judgments, changes to the estimated fair value of the consideration are recorded as an adjustment to goodwill or the underlying asset value. Where the effect of the time value of



money is material, provisions are adjusted to reflect their present value, and the interest element arising on discounting the liability is recorded as interest payable in the profit and loss account as it unwinds. At December 31, 2003, the main judgment on a balance recorded for deferred consideration relates to the 1996 acquisition of Krypton.

The deferred consideration of Krypton was revised on April 26, 1996, such that a maximum of 37.5 million ordinary shares would be issued contingent on a change in control of the Company at a share price of not less than 80 pence compounded at an annual rate of 10% (£1.71 as at December 31, 2003), or satisfaction of various conditions and hurdles which lapsed on December 31, 2003. No provision for deferred consideration has been recognized as at December 31, 2003 under U.K. GAAP.

### Contingent Liabilities

Provisions for contingent liabilities are dependent upon estimates and assessments of whether the criteria for recognition have been met, including estimates by the Directors as to the probable outcome and the amount of the potential cost of resolution. The Company follows the guidance for identification and recognition of such provisions in accordance with U.K. GAAP. The Company is currently involved in certain legal proceedings as discussed in "Item 8: Financial Information – Legal Proceedings". As at December 31, 2003, no costs have been accrued in relation to these proceedings because the Company does not believe that the proceedings will have a material adverse effect on the Company's consolidated financial position. Any estimate for such an accrual would be developed in consultation with external legal advisors handling the Company's defense in these matters and would be based upon an analysis of potential outcomes. It is possible that future results of operations could be materially affected by changes in our assumptions.

## OPERATING RESULTS

### Overview

The following table sets forth selected items of the Company's consolidated income statement:

	Year Ended December 31,		
	2001	2002	2003
	(in £ thousands)		
<b>Results</b>			
Turnover	46,126	69,573	53,152
Operating (loss)/profit	(5,099)	4,716	(39,519)
Retained (loss)/profit	(9,452)	1,109	(43,223)

The Company has only one segment: pharmaceuticals. This reporting system is in compliance with the U.K. GAAP rule SSAP 25; Segmental Analysis and also reflects the Company's internal financial reporting and the predominant sources of risks and returns in its business.

The Company's revenues are principally generated from three sources:

- contract development and licensing, including milestone payments and research and development costs recharged,
- royalties receivable from sales by third parties of products developed by the Company, and
- manufacturing and distribution related revenue.

Historically, the revenue contribution of each of the Company's revenue sources has varied from period to period. This is especially true of contract development and licensing revenues, the level of which may fluctuate, depending on a number of unpredictable factors, including scientific developments, the ability of the Company to find suitable partners, the timing of the negotiation and conclusion of agreements with such partners, the timing of regulatory approvals, the market introduction of new products and other factors. As a result, year-to-year

comparisons of the

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

Company's revenues may be materially distorted. See "Item 3: Key Information Risk Factors The Company's results of operations tend to fluctuate" for more information on factors influencing the level of the Company's revenues.

Each of the Company's revenue sources yields significantly different gross margins. Accordingly, the comparability of gross margins from period to period is materially affected by the revenue mix in each period. For example, royalty revenues generally result in higher gross margins than contract development and licensing revenues. The Company pursues different strategies with respect to its various revenue sources. In respect of contract development and licensing revenue, the Company generally endeavors to recover its direct costs, its objective being to generate long-term profits from royalties on successful product commercializations.

After cost of sales, the Company's costs principally comprise research and development expenses, administration expenses, selling and marketing expenses, the costs of the corporate offices and interest expense. As the majority of the Company's expenses are incurred in Switzerland, France and the United States, whereas the Company's revenues are substantially denominated in U.S. dollars, the Company's results of operations, as reported in pounds sterling, may be materially influenced by exchange rate movements. To minimize the impact of any fluctuations, the Company's policy has historically been to maintain natural hedges. Where it has not been possible to use natural hedges, currency options, accrual forward options and currency contracts are used. Foreign currency exchange movements did not have a material impact on the results of operations during any of the periods presented below.

Inflation did not have a significant impact on the Company's operations during any of the periods presented below.

### Year Ended December 31, 2003 compared with the Year Ended December 31, 2002

The following table sets forth selected items of our consolidated income statement for the two years ended December 31, 2003.

	Year to December 31,	
	2002	2003
	(in £ thousands)	
<b>Consolidated Income Statement</b>		
Turnover	69,573	53,152
Cost of sales	(24,830)	(29,786)
	44,743	23,366
Gross profit	44,743	23,366
Selling, marketing and distribution expenses	(4,769)	(4,348)
Administration expenses		
Amortization	(6,506)	(6,669)
Other administration expenses including exceptional impairments	(13,686)	(27,474)
	(20,192)	(34,143)
Research and development expenses	(29,285)	(30,520)
Other operating income	14,219	6,126
	4,716	(39,519)
Operating profit/(loss)	4,716	(39,519)
Interest receivable	1,081	1,029
Interest payable	(4,464)	(4,493)
	1,333	(42,983)
Profit/(loss) on ordinary activities before taxation	1,333	(42,983)
Taxation	(224)	(240)
	1,109	(43,223)
Net profit/(loss)	1,109	(43,223)

**Turnover**

The following table breaks down the Company's turnover by revenue source for the two years ended December 31, 2002 and 2003:

	Year ended December 31,	
	2002	2003
(in £ thousands)		
Contract development and licensing	55,441	29,652
Royalties receivable	6,751	18,701
Manufacturing and distribution	7,381	4,799
<b>Total</b>	<b>69,573</b>	<b>53,152</b>

In 2003, turnover decreased by 24% to £53.2 million, compared with £69.6 million in 2002, primarily reflecting lower levels of contract development and licensing revenue.

**Contract Development and Licensing**

The following table breaks down the Company's contract development and licensing revenues for the two years ended December 31, 2002 and 2003:

	Year ended December 31,	
	2002	2003
(in £ thousands)		
Milestone payments	47,736	24,196
Research and development costs recharged	7,705	5,456

Contract development and licensing revenue represents amounts invoiced to customers for services rendered under development and licensing agreements, in accordance with the terms and conditions of the relevant collaborative arrangement, including milestone payments, technology access fees and research and development costs recharged. Such amounts are treated as revenue when the relevant services have been rendered or the specified milestones have been met, to the extent that there are no obligations pursuant to the revenue.

Contract development and licensing revenue decreased by 47% to £29.7 million in 2003, due primarily to a decline in milestone payments received from collaborative partners. Revenues recognized from milestone payments and payments received on the signing of agreements amounted to £24.2 million in 2003 compared with £47.7 million in 2002. The 2003 total included revenue from Endo upon the FDA's formal acceptance for filing of a NDA for DepoDur, Mundipharma for the rights to market and distribute DepoCyt® in most European and Eastern European countries, King for developing and commercializing a modified-release formulation of Altace (ramipril) and the signing of an option agreement in respect of an undisclosed pulmonary product. In addition, SkyePharma received milestones from GlaxoSmithKline and AstraZeneca on the initiation of Phase III clinical trials of Requip® (ropinirole) and Budesonide HFA respectively.

The Company had expected to enter into several new licensing agreements in 2003, in connection with which it would have received substantial milestone payments. These transactions included the licensing of a package of products in the pulmonary field, the licensing of DepoDur for Europe and the licensing of an unnamed pipeline product subsequently filed for approval with the FDA in March 2004. In 2004, the Company was able to successfully complete the licensing of DepoDur for Europe and the licensing of the unnamed pipeline product. In April 2004, SkyePharma announced the licensing of DepoDur for Europe to Medeus and of its dermatology assets, which account for substantially all of the Company's topical drug delivery technologies, to Trigenesis. In May 2004, SkyePharma announced the licensing of an undisclosed cardiovascular product for the U.S. to First Horizon. Milestone payments and payments on signing are expected to continue to be an important component of turnover in the near term.

### *Royalties*

Royalty income represents amounts paid by third parties for the sale of therapeutics based on the Company's drug delivery technologies. Royalties are typically calculated as a percentage of the third parties' net sales of the relevant drugs. Advance royalty payments are treated as deferred income until earned, at which point they are recognized in income. Royalty income almost tripled to £18.7 million, compared with £6.8 million in 2002, following a fourfold increase in 2002. Royalty income in 2003 derived principally from sales of Paxil CR, Xatral® OD, DepoCyt® and Solaraze®.

### *Manufacturing and Distribution*

Manufacturing and distribution revenue principally comprises contract manufacturing fees invoiced to third parties and revenue from the sale of products. Contract manufacturing and distribution revenue decreased by 35% to £4.8 million, compared with £7.4 million in 2002, due principally to the way in which the Company accounts for revenue under the new licensing arrangements for DepoCyt® agreed with Enzon as compared with the previous agreement with Chiron. Revenue from Enzon is split between royalty and manufacturing and distribution income in accordance with the contract. Under the previous arrangements with Chiron the Company recorded its 50% share of sales as manufacturing and distribution income. This category also includes £1.0 million from Kowa under our collaboration on a new lipid lowering agent, NK-104 and £0.9 million in respect of Foradil® Certihaler® for Novartis.

### *Expenses*

#### *Cost of Sales*

Cost of sales consists primarily of the costs of the Company's research and development activities performed on behalf of third parties, including:

the costs of certain clinical trials conducted on behalf of the Company's collaborative partners,

the direct costs of contract manufacturing, and

the direct costs of licensing arrangements and royalties payable.

Cost of sales increased by 20% to £29.8 million in 2003, compared with £24.8 million in 2002. This increase was mainly due to higher levels of royalty payments made to Paul Capital (£2.5 million) under the Company's arrangements to finance the development of DepoDur, Propofol IDD-D and HFA-formoterol and increased manufacturing and distribution costs.

The resulting gross profit decreased by £21.4 million to £22.4 million, primarily as a result of the decreased milestone payments and payments received on the signing of agreements as a consequence of the delays in concluding three key new deals in 2003 and a £4.8 million increase in manufacturing losses. The manufacturing losses arise primarily due to inadequate overhead recovery in the U.S. and Lyon prior to the start of manufacture or the achievement of break-even sales levels of the Company's own products and licensee products.

#### *Selling, Marketing and Distribution Expenses*

Selling, marketing and distribution expenses comprise the costs of marketing the Company's services. Selling, marketing and distribution expenses decreased by 8.8% to £4.3 million, compared with £4.8 million in 2002. This is due principally to the termination of the joint venture with Chiron in respect of DepoCyt®. In 2002, SkyePharma accounted for 50% of the joint venture's selling and marketing costs. During 2003, DepoCyt® has been marketed by Enzon under a new licensing arrangement under which Enzon bears 100% of selling and marketing costs.

*Amortization Expenses*

Amortization expenses include the amortization of intangible fixed assets, including goodwill and intellectual property. Amortization of intangible assets increased slightly by £0.2 million from £6.5 million.

*Other Administration Expenses*

Other administration expenses include the non-product related general and administration costs of the Company. Other administration expenses before exceptionals were £18.0 million in 2003, compared with £13.7 million in 2002. The increase mainly relates to one-off charges, including the cost of reacquiring the DepoCyt® European rights from Elan and writing down the Group's investment in GeneMedix to market value at year-end.

*Exceptional Items*

The exceptional charge of £9.5 million in 2003 includes a restructuring charge of £2.7 million relating to costs in connection with staff reductions arising from the reorganization of the Company's research and development operations and other business functions. The remaining restructuring provision of approximately £1.8 million will be utilized in 2004. The Company expects that a further charge will be recognized in 2004. The 2003 exceptional charge also includes a further non-cash charge of £4.0 million in respect of the impairment of intellectual property and tangible fixed assets related to the reorganization. In addition, £1.6 million relates to a write-down in the value of investments. A further £1.2 million of the charge relates to the settlement of a licensing dispute.

*Research and Development Expenses*

Research and development expenses comprise only costs incurred by the Company in conducting its own research and development projects on existing formulations. Costs incurred in conducting research and development projects for third parties are recorded as cost of sales. Research and development expenses increased by 4.2% to £30.5 million in 2003, compared with £29.3 million in 2002, as contrary to the Company's expectations it was unable to transfer the costs of certain research and development projects to its partners due to the delays to completion of new agreements.

*Other Operating Income*

Other operating income comprises income recognized by the Company under its agreements with Paul Capital. Income is recorded on a "cost to complete" basis over the life of each individual project. This means that the Company takes the risk of project costs exceeding the projections underlying the agreements with Paul Capital.

Paul Capital provided a total of \$30 million between 2000 and 2002, in return for the sale of a portion of the potential future royalty and revenue streams from DepoDur<sup>®</sup>, Xatral<sup>®</sup> OD, Solaraze<sup>®</sup> and DepoCyt<sup>®</sup>. Income of £1.1 million was recognized as Other operating income under this agreement on a cost to complete basis in 2003, compared with £9.7 million in 2002. All of the income under this agreement has now been recognized.

Under a second transaction, Paul Capital provided a further \$30 million during 2002 and 2003, in return for the sale of a portion of the potential future royalty and revenue streams from nine products from the Group's drug pipeline. Income of £5.0 million in 2003, compared with £4.5 million in 2002, was recognized as Other operating income under this agreement on a cost to complete basis. Further details are provided in Note 3 to the Company's Consolidated Financial Statements. Details of the Company's agreements with Paul Capital are explained under "Item 4: Information on the Company Business Operations Collaborative Arrangements Other Collaborative Arrangements."

**Operating Results**

The most significant factor contributing to the Group's operating loss of £39.5 million, compared with an operating profit of £4.7 million in 2002 is the fact that the Company's budget for 2003 had assumed that the Company would receive milestone payments under several licensing agreements that it had expected to enter into in 2003 but that were delayed until 2004. The Company has meanwhile successfully concluded the negotiations for the licensing of DepoDur for Europe and the licensing of an unnamed pipeline product and will record milestone payments received under these agreements in accordance with its revenue recognition policy. The exceptional charge of £9.5 million and the reduction in income being recognized under the Paul Capital agreements of £8.1 million have also contributed to the 2003 loss. The net loss was £43.2 million in 2003, compared with a net profit of £1.1 million in 2002.

Earnings before interest, tax, depreciation and amortization ("EBITDA"), a commonly used performance indicator, amounted to a loss of £26.6 million in 2003 compared with a profit of £17.3 million in 2002. Management believes that EBITDA provides useful information to investors because it provides a clearer picture of the Company's operating performance by excluding items related to the Company's financings and investing activities.

	Year ended December 31,	
	2002	2003
(in £ thousands)		
<b>Reconciliation of retained (loss)/profit to EBITDA</b>		
Retained profit/(loss)	1,109	(43,223)
Interest receivable	(1,081)	(1,029)
Interest payable	4,464	4,493
Taxation	224	240
Depreciation	6,101	6,294
Amortization	6,506	6,669
EBITDA	17,323	(26,556)

**Year Ended December 31, 2002 compared with the Year Ended December 31, 2001****Turnover**

The following table breaks down the Company's turnover by revenue source for the two years ended December 31, 2001 and 2002:

	Year ended December 31,	
	2001	2002
(in £ thousands)		
Contract development and licensing	38,236	55,441
Royalties receivable	1,468	6,751
Manufacturing and distribution	6,422	7,381
Total	46,126	69,573

Turnover increased by 51%, from £46.1 million in 2001 to £69.6 million in 2002. This increase was primarily driven by a substantial increase in milestone payments, the effects of which were partially offset by lower cost reimbursements from third parties for research and development services rendered pursuant to contract development arrangements. In geographic terms, the increase in turnover was due mainly to higher turnover in the United States. The acquisition of SkyePharma Canada Inc. (formerly RTP Pharma Inc.) contributed revenue of £3.9 million.





## Edgar Filing: SKYEPHARMA PLC - Form 20-F

### *Contract Development and Licensing*

The following table breaks down the Company's contract development and licensing revenues for the two years ended December 31, 2001 and 2002:

	Year ended December 31,	
	2001	2002
	(in £ thousands)	
Milestone payments	28,379	47,736
Research and development costs recharged	9,857	7,705

Contract development and licensing revenue increased by 45%, from £38.2 million in 2001 to £55.4 million in 2002, mainly reflecting higher levels of milestone payments received on the signing of agreements. In 2002 milestone payments and payments received on the signing of agreements included revenue from Shire for the rights to market Solaraze® in Europe, Endo for the U.S. and Canadian marketing and distribution rights for DepoDur and Propofol IDD-D and Enzon for the rights to DepoCyt® in North America. Additionally a key milestone payment was received from GlaxoSmithKline for the completion of Phase II clinical trials for ropinirole in November 2002.

### *Royalties*

Royalty income increased substantially, from £1.5 million in 2001 to £6.8 million in 2002, reflecting principally revenues from Paxil CR , which was launched in the United States in April 2002, and an increase in revenues from Xatral® OD and Solaraze®.

### *Manufacturing and Distribution*

Manufacturing and distribution revenue increased by 15%, from £6.4 million in 2001 to £7.4 million in 2002. The 2002 figure comprises contract manufacturing revenues of £5.4 million and SkyePharma's share of DepoCyt® sales, which amounted to £2.0 million. Included in contract manufacturing revenue in 2002 is some £1.8 million in respect of Foradil® DPI for Novartis and £1.0 million from Kowa under our collaboration on formulations of a new lipid lowering agent, NK-104.

### *Expenses*

#### *Cost of Sales*

Cost of sales increased by 32%, from £18.8 million in 2001 to £24.8 million in 2002, reflecting the higher level of activity and increased number of projects currently being undertaken. As a percentage of turnover, cost of sales decreased from 41% to 36%. The decrease of costs of sales relative to turnover reflects an increase in the proportion of milestone payments and royalty revenue which typically offer higher margins than other types of revenue.

#### *Selling, Marketing and Distribution Expenses*

Selling, marketing and distribution expenses were £4.8 million in 2002, unchanged compared to 2001, of which, £2.8 million related to product sales such as DepoCyt® and £2.0 million related to the expenses of the business development offices in New York, Muttentz and Japan.

#### *Amortization Expenses*

Amortization of intangible assets increased by 50%, from £4.3 million in 2001 to £6.5 million in 2002, which includes an increase in the amortization of goodwill of £1.5 million relating to the acquisition of SkyePharma Canada Inc. and the drug delivery business of Bioglan AB. In addition, the increase reflects increased amortization charges on intellectual property with respect to DepoCyt® licenses.

*Other Administration Expenses*

Other administration expenses increased by 12%, from £12.2 million in 2001 to £13.7 million in 2002. The increase mainly reflects the administration costs of SkyePharma's new operations in Canada and Sweden, which were fully consolidated for the first time in 2002 and increased professional fees for transactions undertaken during the year.

*Research and Development Expenses*

Research and development expenses increased by 63%, from £17.9 million in 2001 to £29.3 million in 2002, due to increased expenditure on projects such as DepoDur, HFA-formoterol, Budesonide-HFA and Propofol IDD-D.

*Other Operating Income*

Other operating income increased by 124% from £6.3 million in 2001 to £14.2 million in 2002. During 2002, SkyePharma received £6.4 million of cash under the 2001 agreement and recognized income of £9.7 million on a cost to complete basis which was in line with expenditure on the project. Royalty payments are not required to be made to Paul Capital under this agreement until 2003. In addition, SkyePharma received £11.6 million of cash and recognized income of £4.5 million under the 2002 agreement on a cost to complete basis. During the year royalty payments of £0.7 million were made to Paul Capital under this agreement. Further details are provided in Note 3 of the Consolidated Financial Statements.

*Operating Results*

As a result of the factors described above, the Company achieved an operating profit of £4.7 million in 2002, compared with an operating loss of £5.1 million in 2001.

In 2002, SkyePharma achieved its first full year profit after tax of £1.1 million, compared with a net loss of £9.5 million in 2001. The Group also achieved a profit on ordinary activities before tax of £1.3 million in 2002, after a net interest payable charge of £3.4 million (2001: £3.7 million), which compares with a loss on ordinary activities before tax of £9.4 million in 2001. The earnings per share for the year increased by 2.0 pence per share to 0.2 pence per share (2001: 1.8 pence loss per share). Earnings before Interest, Tax, Depreciation and Amortization ("EBITDA") for 2002 is £17.3 million compared with £3.4 million in 2001. EBITDA is a non-GAAP performance measure which the Group considers to improve the understanding of operating performance. Under U.S. GAAP, the Company recorded a loss of £45.3 million in 2002, compared with a loss of £43.9 million in 2001.

	Year ended December 31,	
	2001	2002
	(in £ thousands)	
<b>Reconciliation of retained (loss)/profit to EBITDA</b>		
Retained (loss)/profit	(9,452)	1,109
Interest receivable	(1,251)	(1,081)
Interest payable	4,951	4,464
Taxation	75	224
Depreciation	4,778	6,101
Amortization	4,327	6,506
EBITDA	3,428	17,323

**LIQUIDITY AND CAPITAL RESOURCES**

The following is a summary of the Group's contractual cash obligations as of December 31, 2003:

	<b>Payments Due by Period</b>				
	<b>Total</b>	<b>&lt; 1 year</b>	<b>1-3 years</b>	<b>4-5 years</b>	<b>After 5 years</b>
	(in £ thousands)				
Bank overdrafts	1,198	1,198			
Bank loans	4,265	2,342	1,877	46	
Secured mortgage	7,543	271	541	543	6,188
Chiron promissory note	559	559			
Finance leases	366	160	187	19	
Accrued rent	3,459				3,459
Operating leases	31,922	3,460	6,044	5,101	17,317
Convertible bonds (due 2005)	59,400		59,400		
Non-equity Deferred "B" shares	11,310		11,310		
Provisions	285				285
<b>Total Contractual Cash Obligations</b>	<b>120,307</b>	<b>7,990</b>	<b>79,359</b>	<b>5,709</b>	<b>27,249</b>

Capital commitments, contracted for but not provided in the accounts, were £Nil at December 31, 2003 and £0.2 million at December 31, 2002.

The Group does not have any off-balance sheet arrangements that have or are reasonably likely to have a material effect on the Group's financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources.

*Cash requirements*

The Company's largest potential cash obligation in the foreseeable future relates to the Convertible Bonds due 2005 in the amount of £59.4 million. The bonds are convertible at the option of the holder into ordinary shares at a conversion price of 83 pence at any time up to June 19, 2005. Unless previously redeemed or converted, the bonds will be redeemed by the Company at the principal amount on June 19, 2005. The Company is evaluating options in the event that the share price is not in excess of the conversion price of 83 pence prior to this date, including the refinancing of the bonds.

Assuming the conversion or refinancing of the Convertible Bonds due 2005, the Directors believe, taking into account the amounts of cash available, the Company has sufficient working capital for the requirements of the foreseeable future. There can however be no assurance that the bonds will be converted or, if not converted that the Company will be able to refinance the Convertible Bonds due 2005 or that additional funds will be available, on favourable terms or at all, or that such funds, if raised would be sufficient to permit the Company to continue to conduct its operations. For further information, see "Item 3: Key Information Risk Factors".

The current cash balances will enable the Company to selectively develop a number of key projects to a later stage of development prior to licensing out, thereby potentially increasing its share of any profits that these projects may yield. The Company is an emerging pharmaceutical company and expects to continue to absorb cash until products are fully commercialized. Much of the Company's cash requirements are of an investment nature and are to a great extent discretionary. Funds will be used for the Company's own product development efforts and capital expenditure. Capital commitments as at December 31, 2003, amounted to £Nil (2002: £0.2 million).

Future acquisitions or investments, a material decrease in our cash flow from operations or the failure of our collaborative partners to provide funding are factors which could affect our liquidity and working capital. The Company is reliant on collaborative partners and upon its ability to

continue to obtain new development contracts from third parties to further develop and commercialize its drug delivery technologies. See "Item 3: Key Information Risk Factors". The Company is dependent on its Geomatrix and DepoFoam technologies as to which further successful development is uncertain and any failure by the Company's collaborative partners to provide funding, obtain regulatory approvals and conduct marketing activities could adversely affect the Company's business, results, financial condition and liquidity.

*Sources and uses of cash*

	Year ended December 31,		
	2001	2002	2003
	(in £ thousands)		
Net cash inflow from operating activities	5,909	1,552	6,615
Returns on investments and servicing of finance	(1,799)	(3,100)	(3,036)
Taxation	(75)	(224)	(227)
Purchase of tangible and intangible fixed assets	(7,983)	(6,273)	(6,551)
Purchase of fixed asset investments	(8,273)	(6,285)	(5,674)
Acquisitions	1,318	(3,595)	
Cash outflow before use of liquid resources and financing	(10,903)	(17,925)	(8,873)
Management of liquid resources	14,668	(3,872)	183
Financing	(4,891)	21,621	2,818
Decrease in cash	(1,126)	(176)	(5,872)

The Company finances its operations primarily by cash generated from the sale of equity and debt securities, funding provided by collaborative partners and operations.

As discussed above, a significant percentage of the Company's cash resources comprise milestone payments under licensing and marketing agreements between the Company and its collaborative partners. The amount of milestone payments that the Company receives in any given period is influenced by a number of unpredictable factors, including scientific developments, the ability of the Company to find suitable partners, the timing of the negotiation and conclusion of agreements with such partners, the timing of regulatory approvals, the market introduction of new products and other factors. Although the Company is seeking to decrease the proportion of its revenues derived from milestone payments, the uncertainty associated with milestone payments means that there is no assurance that the Company will be able to obtain sufficient funds to satisfy its financing needs.

Net cash inflow from operating activities was £6.6 million in 2003, versus £1.6 million in 2002. The reconciliation of operating (loss)/profit to net cash inflow from operating activities shows a decrease in debtors between 2003 and 2002 of £19.6 million. This mainly reflects the amounts received from Endo and Enzon on January 3, 2003 in respect of contracts signed at the end of December 2002.

During 2003, £7.6 million (\$12.5 million) (2002: £11.6 million (\$17.5 million)) in cash was received under an agreement with Paul Capital by which Paul Capital has provided a total of \$30 million during 2002 and 2003, in return for the sale of a portion of the potential future royalty and revenue streams from nine products from the Company's drug pipeline.

Total cash outflow before use of liquid resources and financing in 2003 was £8.9 million (2002: £17.9 million). Purchases of fixed asset investments totaled £5.7 million (2002: £6.3 million) of which £2.1 million related to Micap plc, £1.5 million to Astralis Ltd, £1.2 million to Vital Living Inc and £0.9 million was spent on the purchase of SkyePharma shares as part of the Group's hedging strategy for share scheme based remuneration.

Purchases of tangible and intangible fixed assets totaled £6.6 million (2002: £6.3 million). The Company's cash position including short-term bank deposits at December 31, 2003 amounted to £23.2 million (2002: £28.1 million) (£22.0 million net of overdrafts (2002: £28.1 million)).



*Debt instruments, guarantees and related covenants*

At December 31, 2003, the Company had short-term borrowings, including obligations under finance leases, amounting to £4.5 million (2002: £2.9 million) and long-term borrowings, including obligations under finance leases and Convertible Bonds due 2005, amounting to £68.2 million (2002: £66.7 million).

On June 16, 2000, the Company issued £59.4 million 6% Convertible Bonds due 2005. The Bonds are convertible at the option of the holder into ordinary shares at a conversion price of 83 pence at any time up to June 19, 2005. Unless previously redeemed or converted, the Bonds will be redeemed by the Company at their principal amount on June 19, 2005.

In April 2004, the Group issued £20 million 6% Convertible Bonds, with a first put after five years by the holder of the bonds, and a final maturity of May 2024. The bonds are convertible at the option of the holder into SkyePharma ordinary shares at a conversion price of £1.00 at any time prior to maturity. Unless previously redeemed or converted, the bonds will be redeemed by the Group at their principal amount in May 2024. The Convertible Bonds due 2005 existing at December 31, 2003, due in June 2005, were not affected by this transaction.

At December 31, 2003, the Group had a property mortgage facility with the Basellandschaftliche Kantonalbank of £7.5 million (CHF 16.7 million). The mortgage is in two tranches, both secured by the assets of Jago and guaranteed by SkyePharma. The first tranche of £3.2 million (CHF 7.0 million) bears interest at 3.75% and is repayable by installments over 21 years semi-annually. The second tranche of £4.3 million (CHF 9.7 million) bears interest at 3.0% and is repayable by instalments over 51 years.

Included within bank loans, the Basellandschaftliche Kantonalbank has extended loans of £0.9 million (CHF2 million) and £0.7 million (CHF 1.5 million). These loans are renewable annually and bear interest at 6.5% and 6.0%, respectively. The bank loans are all secured on the assets of Jago and are guaranteed by SkyePharma.

At December 31, 2003, the Group had a loan with GE Capital Corp of £2.7 million (\$5 million). The loan is secured by certain assets of SkyePharma Inc., SkyePharma US Inc. and SkyePharma. The loan bears interest at 8% and is repayable by instalments from 2004 until between 2005 and 2007.

At December 31, 2003, the Group had an overdraft facility of £1.4 million (CHF 3 million) (2002: £1.3 million) with the Basellandschaftliche Kantonalbank, secured on the assets of Jago and guaranteed by SkyePharma.

At December 31, 2003, the Group had a promissory note with Chiron of £0.6 million (\$1 million) which formed part of the consideration for the reacquisition of the U.S. DepoCyt® marketing, distribution and sales rights. The promissory note is repayable in June 2004, bearing interest at LIBOR plus 300 points and is guaranteed by SkyePharma.

*Financial Instruments*

The Group holds financial instruments to finance its operations and to manage the currency risks that arise from these operations. Further information on these financial instruments is set out in Note 26 of the Notes to SkyePharma's Consolidated Financial Statements included in Item 18 of this Form 20-F.

**PRINCIPAL DIFFERENCES BETWEEN U.K. AND U.S. GAAP**

The Company's financial statements have been prepared in accordance with U.K. GAAP, which differs in certain respects from U.S. GAAP. See Note 31 of the Notes to the Company's Consolidated Financial Statements included in Item 18 of this Form 20-F for a reconciliation of the Company's net income for the three years ended December 31, 2003 and shareholders' funds as of December 31, 2003 and 2002 from U.K. GAAP to U.S. GAAP.

The reconciliation of the Company's net income for each of 2003 and 2002 primarily reflects differences in the accounting principles under U.K. GAAP and U.S. GAAP with respect to revenue

recognition and the sale of royalty interests. The reconciliation of the Company's net income for 2001 mainly reflects differences in the accounting treatment under U.K. GAAP and U.S. GAAP governing write-offs of acquired in-process research and development costs and revenue recognition.

The reconciliations of the Company's shareholders' funds as of December 31, 2003 and 2002 primarily reflect differences in the accounting principles under U.K. GAAP and U.S. GAAP in respect of revenue recognition, goodwill, differences in the accounting for shares and warrants to be issued, deferred shares and shares issued to Dr. Gonella, and the different treatment of contingent consideration charged to goodwill reserve.

#### **NEW ACCOUNTING STANDARDS NOT YET ADOPTED**

The Company will be required to prepare consolidated financial statements under International Financial Reporting Standards ("IFRS") from January 1, 2005 and to restate the 2004 financial statements for comparison.

The transition to IFRS could have a material impact on the Company's financial position and reported results from this date. The Company expects to quantify the potential impact during 2004, and has formed a project team to manage its transition to IFRS.

In November 2002, the Emerging Issues Task Force (EITF) reached a consensus on EITF 00-21, "Revenue Arrangements with Multiple Deliverables," related to the timing of revenue recognition for arrangements in which goods or services or both are delivered separately in a bundled sales arrangement. The EITF requires that when the deliverables included in this type of arrangement meet certain criteria they should be accounted for separately as separate units of accounting. This may result in a difference in the timing of revenue recognition, but will not result in a change in the total amount of revenue recognized in a bundled sales arrangement. The allocation of revenue to the separate deliverables is based on the relative fair value of each item. If the fair value is not available for the delivered items then the residual method must be used. This method requires that the amount allocated to the undelivered items in the arrangement is their full fair value. This would result in the discount, if any, being allocated to the delivered items. This consensus is effective prospectively for arrangements entered into in fiscal periods beginning after June 15, 2003, which, for the Group, is January 1, 2004. The Group is assessing the impact of this interpretation.

In January 2003, the FASB issued Interpretation No. 46, "Consolidation of Variable Interest Entities" (FIN 46) and in December 2003 issued a revision of this interpretation. Under this interpretation, certain entities known as "Variable Interest Entities" (VIE) must be consolidated by the "primary beneficiary" of the entity. The primary beneficiary is generally defined as having the majority of the risks and rewards arising from the VIE. For VIEs in which a significant (but not majority) variable interest is held, certain disclosures are required. The Group is in the process of assessing the impact of this interpretation as it will be effective for the Group beginning January 1, 2004. The effect of this interpretation could be that minority investments that the Group holds in certain companies and which it is also the major provider of development services may required to be consolidated if, within the definitions of the interpretation, the Group maintains the majority of the risks and rewards of this third-party entity.

In May 2003, the FASB issued FAS 150, "Accounting For Certain Financial Instruments with Characteristics of both Liabilities and Equity" (FAS 150). This standard establishes how an issuer classifies and measures certain financial instruments with characteristics of both liabilities and equity and requires that an issuer classify a financial instrument that is within its scope as a liability or an asset in some circumstances. FAS 150 will be effective for financial instruments entered into or modified after May 31, 2003, and otherwise is effective for the group for periods beginning after June 10, 2003. The Group believes that the adoption of this standard will not have a material effect on the group's results of operation or financial position.

**RESEARCH AND DEVELOPMENT, PATENTS AND LICENSES**

For a discussion of the Company's research and development activities, see "Item 4: Information on the Company Business Operations Research and Development" and information on patents and licenses, see "Item 4: Information on the Company Business Operations Patents and Proprietary Rights".

**TREND INFORMATION**

The Company's results of operations have fluctuated materially on a monthly, half yearly and yearly basis, partly as a result of acquisitions and partly due to the timing of contract development and licensing revenues. Therefore, period-to-period and period-on-period comparisons are not meaningful at this stage in the Company's development. The Company believes that it will continue to experience fluctuations in its results of operations in the near to medium term.

**Item 6: Directors, Senior Management and Employees****Directors and Senior Management**

Name	Age	Position
Ian Gowrie-Smith <sup>(4)</sup>	56	Chairman
Michael Ashton <sup>(1)</sup>	58	Chief Executive Officer
Donald Nicholson <sup>(1)</sup>	46	Finance Director and Executive Director
Air Chief Marshal Sir Michael Beavis <sup>(2)(3)</sup>	74	Senior Independent Non-Executive Director
Dr. David Ebsworth <sup>(2)(3)</sup>	49	Non-Executive Director
R. Stephen Harris <sup>(3)(4)</sup>	61	Non-Executive Director
Dr. Keith Mansford <sup>(3)</sup>	72	Non-Executive Director
Dr. Argeris (Jerry) Karabelas <sup>(2)(4)</sup>	51	Non-Executive Director
Toraio Yamamoto	61	Non-Executive Director

(1) Member of Executive Committee.

(2) Member of Audit Committee.

(3) Member of Remuneration Committee.

(4) Member of Nomination Committee.

The following information is provided as at June 24, 2004, the latest practicable date prior to the filing of this Report.

*Ian Gowrie-Smith* became Non-executive Chairman on June 23, 2004, having been Executive Chairman since January 1995. From January 1995 to November 1998 he was also Chief Executive Officer of the Company. Mr Gowrie-Smith has more than 17 years of management experience in the pharmaceutical industry and was responsible for the founding and subsequent flotation of Medeva plc. He is non-executive chairman of Tiberon Metals Limited, Triple Plate Junction PLC and Micap PLC. He graduated with a Bachelor of Commerce degree from the University of Melbourne in 1970.

*Michael Ashton* was named Chief Executive Officer of the Company in November 1998. He joined the Company in January 1997 as Chief Executive Officer of Jago, was appointed to the Board in March 1997 and was named Chief Operating Officer of the Company in May 1998. He has over 31 years of experience in the pharmaceutical industry having worked for Merck Inc., Pfizer Inc., Purepac Inc. and prior to this appointment, Faulding Inc., where Mr Ashton was chairman, president and CEO. He is a non-executive director of Transition Therapeutics Inc., Astralis Limited and Vital Living Inc. He obtained a B. Pharm degree from Sydney University in 1968 and an MBA from Rutgers University in 1974.

*Donald Nicholson* was named Finance Director in March 1997. He joined the Company in February 1996 as Chief Financial Officer and was appointed to the Board in March 1997. He has





over 18 years of experience in the healthcare industry including Wellcome plc and Corange Ltd, the holding company of Boehringer Mannheim and DePuy, where he was corporate strategy and finance director. He is a member of the Institute of Chartered Accountants of Scotland and obtained a B. Com (Hons) degree from the University of Edinburgh in 1980.

*Air Chief Marshal Sir Michael Beavis* was appointed to the Board in 1989 and was appointed Senior Independent Non-executive Director in May 2001. Sir Michael entered the Royal Air Force in 1947 and retired in 1987, his last appointment being Deputy Commander-in-Chief Allied Forces Central Europe, NATO. He is a defence consultant with Burdeshaw Associates, USA, a Companion of the Chartered Management Institute, a Freeman of the City of London and a Liveryman in the Guild of Air Pilots and Navigators.

*Dr David Ebsworth* was appointed to the Board in April 2002. Dr Ebsworth has over 20 years of pharmaceutical industry experience. He provides consultancy services to a variety of clients including venture capital companies. He was chief executive officer of Oxford GlycoSciences PLC until May 2003. Prior to this he held the position of president and general manager of the Pharmaceutical Business Group for Bayer AG in Leverkusen, Germany, and has also worked for Bayer AG in a series of global positions in Canada, Europe and the United States. Dr Ebsworth is non-executive chairman of Wilex AG and a non-executive director of Intercell AG, Betapharm GmbH and CuraGen Corporation and held the same office, until 1998, with Schein Pharmaceutical, Inc. (now known as Watson Pharmaceuticals, Inc).

*R Stephen Harris* was appointed to the Board in November 1995. He has 40 years' commercial experience in the pharmaceutical industry, having worked for ICI Pharmaceuticals, Merck, Eli Lilly, Boots, Reckitt & Colman and Gensia; and was director of Development and Licensing with Medeva plc. He is non-executive chairman of Proteome Sciences plc, Sinclair Pharma plc and Conve Ltd and non-executive director of Advanced Medical Solutions Group plc, Microscience Ltd, Prophilian plc and GeneMedix plc. He is a member of the Pharmaceutical Society of Great Britain and graduated with a B.Sc in Pharmacy from the University of London in 1964.

*Dr Argeris (Jerry) Karabelas* was appointed to the Board in November 2000. Dr Karabelas has more than 21 years' experience in the pharmaceutical industry having spent the majority of his career with SmithKline Beecham. Dr Karabelas is a partner at Care Capital LLC. He was previously the CEO of Novartis Pharma AG where he had responsibility for pharmaceuticals, R&D, consumer products, and the generics business. He is also an external director of Human Genome Sciences, Fox Chase Cancer Center and the International Partnership for Microbicides. He is also a director of NitroMed Inc., Halsey Pharmaceuticals, Inotek, Anadys, Renovo and a member of the scientific advisory board of Epigenesis. He received a Ph.D in Pharmacokinetics from the Massachusetts College of Pharmacy in 1979.

*Dr Keith Mansford* was appointed to the Board in March 1996. He has over 45 years' experience in the pharmaceutical and biotechnology sectors, principally with Beecham Group and SmithKline Beecham. From 1984 to 1992 Dr Mansford was chairman of Research and Development at Beecham Group and subsequently SmithKline Beecham plc. He is a non-executive director of Sepracor Inc, chairman of Mansford Associates, an international healthcare consultancy, chairman of Protomix Inc, a biotech company based in New Zealand, and professor of Metabolic Biochemistry at the University of Buckingham. He obtained a B.Sc in Chemistry and an M.Sc in Biochemistry from the University of Durham and a Ph.D in Biochemistry from the University of London.

*Torao Yamamoto* was appointed to the Board in October 2002. Mr. Yamamoto is the senior managing director of the Pharmaceutical Division of Kowa Company Limited in Japan. Mr. Yamamoto has been with Kowa, a Japanese conglomerate with interests in pharmaceuticals, textiles, electronics, optics and chemicals, since 1965. He has held management positions in Japan and the United States, where he was general manager of all Kowa's operations for four years until June 1998. He currently serves on the board of directors of Kowa Company Limited, Kowa

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

Pharmaceutical Europe, Ltd., and Kowa Research Europe, Ltd. He graduated in March 1965 with a Bachelor's degree in Business Administration from Kobe University of Commerce in Japan.

Mr. Yamamoto was appointed a Non-executive Director in October 2002 pursuant to an agreement between the Company and Kowa.

There are no other arrangements or understandings with major shareholders, customers or suppliers or others pursuant to which any person was selected to serve as a director or senior manager.

There are no provisions within the directors' service contracts that provide for any benefit to accrue to any director upon termination of employment save that salary may be paid in lieu of notice.

### COMPENSATION

In 2003, the Company paid £1,695,000 in aggregate to its Directors (10 persons).

The following table provides certain information regarding the compensation paid to Directors in 2003.

Name	Salary	Bonus	Pension Benefits	All Other Compensation <sup>(1)</sup>
(In £ thousands)				
Ian Gowrie-Smith	450		56	19
Michael Ashton <sup>(2)</sup>	396	59	50	54
Donald Nicholson	220	44	28	10
Air Chief Marshal Sir Michael Beavis	53			
Dr David Ebsworth	49			
Stephen Harris	47			
Dr Keith Mansford	46			
Walter Zeller <sup>(3)</sup>	25			
Dr Argeris (Jerry) Karabelas	47			
Torao Yamamoto	42			

(1) All other compensation includes company car allowance and medical insurance for directors, officers and their families.

(2) All other compensation additionally includes living allowance.

(3) Mr. Zeller retired as a Director on May 28, 2003.

For further information on share options granted, see "Outstanding Options" below.

The Remuneration Committee of the Board of Directors administers a bonus plan for the Company's Executive Directors and officers. Bonuses are paid at the discretion of the Remuneration Committee, in recognition of the individual's contribution to the success of the Company and the achievement of specified objectives. In 2003 the primary performance targets were a combination of objective corporate, divisional and specific individual targets. A fundamental part of the annual bonus plan is the requirement that a stated proportion of any cash bonus awarded under the bonus plan each year be deferred through the Company's Deferred Share Bonus Plan introduced in 2001. The Plan is designed to align the interests of participants with those of the shareholders by encouraging Executive Directors and officers to build up and maintain shareholdings which are meaningful in the context of their remuneration. The minimum deferred proportion of the bonus is currently set at 50% and Executives voluntarily decided to receive all 2003 bonus payments in shares to demonstrate their ongoing commitment to, and confidence in, the Company. The Company currently provides one matching share (each a "Matching Share") for each share acquired by a participant pursuant to the plan (each an "Executive Share"). Each Matching Share will be released three years after it is issued provided that the Executive Director or officer remains in employment and the corresponding Executives Shares have not been sold. The release of



Matching Shares issued prior to 2004 is not subject to additional performance criteria because the Remuneration Committee believes that the performance conditions which have to be satisfied for the payment of any bonus are sufficiently challenging to justify the total bonus payment and additional Matching Shares. However, in line with current UK corporate governance best practice and the wishes of the majority of the Company's shareholders, the Company is proposing to apply performance conditions to the Matching Shares for the 2004 bonus.

## **PENSION AND SAVINGS PLANS**

The Company operates various defined contribution plans for its employees in the United Kingdom, Switzerland, the United States, Canada and Sweden. The Company's contributions to these plans are charged to the income statement in the year to which they relate, and the assets are held in separate trustee administered funds. In 2003, the Company contributed £1,769,000 (2002: £1,525,000) to pension and savings plans and a provision of £285,000 (2002: £201,000) is included within provisions for liabilities and charges. See Note 18 of the Notes to SkyePharma's Consolidated Financial Statements included in Item 18 of this Form 20-F.

The Company operates an unfunded defined benefit scheme in respect of its employees in France, based on the national collective agreement of the pharmaceutical industry.

At December 31, 2003, a valuation of the scheme was performed by professionally qualified actuaries, Société de Prospective Actuariat et Conseil, on the present value of the accrued liabilities calculated under the projected unit method. The valuation showed a pension liability of £603,000.

## **BOARD PRACTICES**

The Company's Articles of Association provide that, except as otherwise provided in the Articles or unless otherwise determined by ordinary resolution of the Company, the Board of Directors shall consist of not less than three directors. Directors of U.K. companies do not generally have fixed terms of office. The Articles provide that at each Annual General Meeting, a number of directors equal to as close as possible (but not exceeding) one-third of the directors must retire from office by rotation, based principally on length of term of office, and are eligible for re-election. Directors may be appointed by the Company by ordinary resolution of the shareholders. In addition, the Board of Directors may appoint directors to fill vacancies or as additional directors. Any director so appointed by the Board of Directors must retire from office at the next Annual General Meeting but is then eligible for re-appointment by the shareholders at that meeting. In accordance with best practice in the United Kingdom, Sir Michael Beavis was appointed Senior Independent Non-executive Director in May 2001.

The Board has an Executive Committee, an Audit Committee, a Remuneration Committee and a Nomination Committee. The Executive Committee is responsible for the executive management of the Company. It is chaired by the Chief Executive Officer and is comprised of the Executive Directors. The Executive Committee comprises all of the Company's senior management. The Executive Committee generally meets monthly between Board meetings.

The Audit Committee is responsible for oversight of auditors, pre-approving all audit and non-audit services, reviewing and appraising the Company's financial reporting practices and procedures, the adequacy of its system of internal accounting control, reviewing the auditor's report describing all critical accounting policies and practices, all alternative treatments within GAAP for material items discussed with management and other material written communications and any matters raised by its independent auditors. It also is responsible for reviewing the half-year and full-year results of the Company and its Interim and Annual Reports and Accounts prior to their submission to the full Board. The Committee reviews the cost-effectiveness, independence and objectivity of the external auditors and also pre-approves all permitted non-audit expenditure incurred with the auditors. It meets formally at least three times a year.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

The Remuneration Committee is responsible for approving the remuneration and other benefits, including pension contributions, bonus payments, share options and severance payments, of the Executive Directors and other members of senior management. The Remuneration Committee is comprised of the Non-executive Directors identified above and is chaired by Sir Michael Beavis.

The Nomination Committee is responsible for making recommendations to the Board on any appointment to the Board. The Nomination Committee is comprised of the Chairman and the Non-executive Directors identified above.

### EMPLOYEES

The following table shows the distribution of the year end number of employees for the last three fiscal years by activity and geographic location:

	Year ended December 31,		
	2001	2002	2003
<b>By category of activity:</b>			
Corporate Management and Administration	68	92	85
Marketing operations	11	13	12
Research and Development	215	239	212
Manufacturing Operations	151	155	157
	445	499	466
<b>By geographic location:</b>			
U.K.	18	18	19
Switzerland	133	126	140
France	124	131	141
Sweden		38	29
U.S. and Canada	170	186	137
	445	499	466
<b>Number of employees with scientific qualifications:</b>			
PhD's, masters or medical degrees	74	89	59
Scientists (including PhD's, masters or medical degrees)	229	267	235

The Company believes that it has good relations with its employees and labor unions.

### SHARE OWNERSHIP

The following table sets out the interests of Directors in the ordinary shares of the Company (including the interests of their immediate families and persons connected with the Directors) as at June 24, 2004.

Name	Number of ordinary shares	Percentage of Issued share capital
Ian Gowrie-Smith	8,539,474	1.372%
Michael Ashton	360,892	0.058%
Donald Nicholson	279,798	0.045%
Air Chief Marshal Sir Michael Beavis	210,297	0.034%
Dr David Ebsworth	45,000	0.007%
Stephen Harris	131,083	0.021%

Edgar Filing: SKYEPHARMA PLC - Form 20-F

<b>Name</b>	<b>Number of ordinary shares</b>	<b>Percentage of Issued share capital</b>
Dr Argeris (Jerry) Karabelas <sup>(1)</sup>	26,667	0.004%
Dr Keith Mansford	67,943	0.011%

(1) Includes ordinary shares represented by ADSs. Each ADS represents ten ordinary shares.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

In addition to the interests shown above, Mr. Ian Gowrie-Smith had a beneficial interest in 20,000 Convertible Bonds, issued by the Company.

The aggregate number of ordinary shares held by the Directors listed in the table above at June 24, 2004 was 9,661,154, representing 1.55% of the total ordinary shares outstanding.

The aggregate number of ordinary shares underlying the Company's outstanding options and long-term incentive plan awards as of June 24, 2004 was 54,076,340.

### Share Option Plans

The Company has five share option schemes (together, the "Option Schemes"): grants between 1996 and 1998 were made under the 1988 Executive Share Option Scheme and the European and North American Scheme and grants from April 1999 were made under the SkyePharma PLC 1999 Share Option Scheme, the European and North American 1999 Scheme and the SkyePharma Holding Inc 1999 Stock Option Plan for SkyePharma Inc. Employees.

Executive Directors and senior executives participate in the SkyePharma PLC 1999 Share Option Scheme, the European and North American Scheme and the SkyePharma Holdings Inc. 1999 Share Option Plan as appropriate. Following publication in March 2001 of revised Association of British Insurers guidelines for Share Incentive Schemes, the Board gained shareholder approval to make certain changes to the SkyePharma PLC 1999 Share Option Scheme and the SkyePharma Holdings Inc. 1999 Share Option Plan at the Annual General Meeting of the Company in June 2001. In particular, the individual participation limits of 200% of remuneration and the performance conditions were amended so that exercise is dependent upon total shareholder return performance against a peer group of companies. All options granted to Executive Directors and senior executives during 2003 were made on this basis and vest after three years on a scale between 0% and 100% depending on the Company's performance relative to the performance against the comparator group of companies. Options granted in 2003 and subsequent years will not be re-tested following vesting. If the stringent performance requirements are not met at the end of the performance period, all options will lapse.

There are two types of options: options and Super Options. With respect to options, prior to 2001 individual participation limits under the schemes were set at four times individual remuneration. Options granted under the schemes are granted at the market price ruling at the date of grant, are exercisable after three years and up to a maximum of 10 years from date of grant. Options granted under each of the schemes may be exercised only if, over a period of three consecutive years, the shareholder return of the Company exceeds the growth in FTSE All Share Index over the same period. Prior to 2001, the individual participation limits for Super Options were set at eight times remuneration. Super Options, also granted at the market price ruling at the date of grant, are exercisable after five years and are subject to more challenging performance conditions based upon top quartile performance in the FTSE 250 Index.

The Company has decided within the current rules of the SkyePharma PLC 1999 Share Option Scheme normally to transfer responsibility for the employer's national insurance contributions on the gain on the exercise of unapproved options to the option-holder.

### *SkyePharma PLC 1999 Share Option Scheme*

The SkyePharma PLC 1999 Share Option Scheme (the "Scheme") is divided into two parts, the first of which is approved by the Inland Revenue and the second of which is unapproved. The unapproved part is designed for the grant of options to employees, the value of which may exceed the approved limit of £30,000. Except to the extent required to obtain Inland Revenue approval, the two parts of the Scheme are similar in all material respects.

The Scheme is governed by the Rules of the Scheme and is administered by the Board of Directors of the Company. Eligibility for participation in the Scheme is limited to those employees of SkyePharma, including Directors, who work for SkyePharma at least 25 hours per week, as may



from time to time be invited to participate by the Board. No Director or employee is entitled as of right to participate in the Scheme.

Options may be granted under the Scheme within six weeks of the day on which the Company first announces its annual or interim results in any year in which the Scheme is in operation or any date on which the Directors determine that exceptional circumstances exist which justify the grant of options at that date. No consideration is payable on the grant of an option. An option may not be granted to an individual selected to participate if the total subscription price thereunder would exceed 200% of the participant's remuneration in that year. Remuneration includes salary, commission and bonuses, but excludes benefits in kind. In the case of the approved part of the Scheme, participants may only be granted options up to a value of £30,000. The Directors will only grant options to replace those already exercised if they are satisfied that there has been sustained improvement in the performance of the Company over not less than a two to three year period prior to such grant. Benefits under the Scheme are not pensionable.

The price per ordinary share at which a participant may acquire ordinary shares (the "Option Price") on the exercise of an option will be at the discretion of the Board, but shall not be less than the market value (as defined in the Rules) of an ordinary share at the date of grant and shall not in any event be less than the nominal value of an ordinary share.

Options granted pursuant to the Scheme may not be exercised prior to the third anniversary of their grant and must be exercised before the expiry of ten years from the date of grant. Super Options may not be exercised prior to the fifth anniversary of their grant and must be exercised before the expiry of ten years from the date of grant. Options may be exercised in whole or in part in respect of any number of ordinary shares subject to a minimum of 1,000 ordinary shares. An option granted under the Scheme may not be exercised unless the relevant condition, as specified by the Directors or a committee thereof and notified to the participant no later than the date of grant, is satisfied. In the case of a Super Option, the performance condition specified by the Directors will be more challenging and in accordance with criteria recommended by the Association of British Insurers.

If a participant leaves the service of the Company by reason of injury, disability, redundancy or normal retirement, or because the company by which such participant is employed ceases to be a member of the Company, such participant will be entitled to exercise any options in accordance with the rules of the Scheme. If a participant leaves the service of the Company by reason of death, such participant's personal representative will be entitled to exercise any options within 12 months following the date of such participant's death. If a participant leaves the service of the Company for any reason other than the foregoing, in respect of option grants prior to 2001 such participant will be entitled to exercise any options within six months of leaving the service of the Company. For options granted during 2001 and subsequently, the options would normally lapse.

If an offeror obtains control of the Company on the occurrence of (i) a general offer to acquire the whole of the ordinary share capital of the Company, (ii) pursuant to an offer, an offeror becoming entitled to acquire the shares under Sections 428-430 of the Companies Act 1985 (the "Act") or (iii) a compromise or arrangement being sanctioned by the Court under Section 425 of the Act, then an option holder and the offeror may agree that the options held can be exchanged for equivalent options in the offeror. Alternatively, if an offeror gains control pursuant to either a general offer or a compromise or arrangement pursuant to Section 425 of the Act, then the option holder may in the case of a general offer, exercise his options within six months following the later of the date of the acquisition or the date upon which the offer becomes unconditional, or in the case of a court order sanctioning a compromise or arrangement, within six months of that date.

#### *The European and North American Scheme*

The European and North American Scheme is in all material aspects identical to the SkyePharma PLC 1999 Share Option Scheme, except that eligibility is restricted to employees in Europe and North America. No further grants will be made under this Scheme.

*The SkyePharma Holdings Inc 1999 Stock Option Plan for SkyePharma Inc. Employees*

The SkyePharma Holdings Inc. 1999 Stock Option Plan (the "Plan") is governed by the rules of the Plan and is administered by the Board of Directors of the Company acting through the Remuneration Committee. The Plan is available to all officers and key employees of SkyePharma Holdings Inc. and its subsidiaries who render services which contribute to its management growth or financial success, at the discretion of the Remuneration Committee. No Director or employee is entitled as of right to participate in the Plan.

Options may be granted under the Plan within six weeks of the day on which the Company first announces its annual or interim results in the year which the Plan is in operation or any date on which the Remuneration Committee determines that exceptional circumstances exist which justify the grant of options at that date. An option may not be granted to an individual selected to participate if the total subscription price thereunder exceeds 200% of his remuneration in that year. Remuneration includes salary, commission and bonuses, but excludes benefits in kind.

If an option is to qualify for tax benefits under certain provisions of the U.S. Internal Revenue Code of 1986 as amended ("Incentive Options"), then the aggregate exercise price of options first becoming exercisable in any one calendar year may not exceed U.S.\$100,000.

The price per ordinary share at which a participant may acquire ordinary shares (the "Option Price") on the exercise of an option will be at the discretion of the Remuneration Committee, but shall not (in the case of Incentive Options) be less than the market value (as defined in the rules of the Plan), or (in the case of options which are not Incentive Options) 85% of the market value (as so defined) of an ordinary share at the date of grant and shall not in any event be less than the nominal value of an ordinary share.

Options must be exercised before the expiry of ten years from the date of grant. The earliest date at which an option may be exercised is at the discretion, in each case, of the Remuneration Committee. The Remuneration Committee may, but is not obliged, to impose conditions on the exercise of an option. In exercising its discretion in these respects, the Remuneration Committee will seek to act in the best interests of the Company, having regard to the conflicting requirements of, on the one hand, the custom and practice in the United States with regard to the grant of share options and the expectations of U.S.-based employees, and, on the other hand, the need to operate the Plan in such a way as complies with best U.K. practice.

The lapsing provisions and those relating to change of control under the Plan are in all material respects similar to the provisions of the SkyePharma PLC 1999 Share Option Scheme, as described on page 89.

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

### Outstanding Options

The table below sets forth certain information concerning the options issued to Directors and officers of the Company pursuant to the Company's share option plans as of June 24, 2004. The remaining Directors and officers of the Company have no outstanding ordinary or Super Options.

#### Ordinary Options

Name	Number of ordinary shares underlying Options Granted	Exercise Price	First Exercise Date	Last Exercise Date
Ian Gowrie-Smith <sup>(1)</sup>	1,234,568	81.0p	December 6, 1999	December 6, 2006
	575,539	69.5p	April 19, 2002	April 19, 2009
	1,008,313	80.6p	June 12, 2004	June 12, 2011
	1,178,022 <sup>(3)</sup>	72.3p	April, 12 2005	April 12, 2012
	1,935,484 <sup>(4)</sup>	46.5p	April 7, 2006	April 7, 2013
Donald Nicholson <sup>(1)</sup>	533,333	75.0p	April 29, 1999	April 29, 2006
	86,022	93.0p	March 31, 2001	March 31, 2008
	172,662	69.5p	April 19, 2002	April 19, 2009
	446,650	80.6p	June 12, 2004	June 12, 2011
	521,826 <sup>(3)</sup>	72.3p	April, 12, 2005	April 12, 2012
Michael Ashton <sup>(2)</sup>	946,237 <sup>(4)</sup>	46.5p	April 7, 2006	April 7, 2013
	639,077	93.0p	March 31, 2001	March 31, 2008
	871,451	69.5p	April 19, 2002	April 19, 2009
	868,486	80.6p	June 12, 2004	June 12, 2011
	1,014,661 <sup>(3)</sup>	72.3p	April 12, 2005	April 12, 2012
	1,703,226 <sup>(4)</sup>	46.5p	April 7, 2006	April 7, 2013

(1) 1,234,568 options in respect of Ian Gowrie-Smith and 533,333 in respect of Donald Nicholson were issued pursuant to the Executive Share Option Scheme. This scheme has subsequently expired in respect of further grants and the remainder of these options were granted under the SkyePharma PLC 1999 Share Option Scheme.

(2) 639,077 issued pursuant to the European and North American Scheme. The remainder of Michael Ashton's options are granted under the SkyePharma PLC 1999 Share Option Scheme.

(3) Options granted during 2002.

(4) Options granted during 2003.

#### Super Options

Name	Number of Ordinary Shares Underlying Options Granted	Exercise Price	First Exercise Date	Last Exercise Date
Ian Gowrie-Smith	2,385,009	56.67p	May 25, 2004	May 25, 2009
Donald Nicholson	1,022,147	56.67p	May 25, 2004	May 25, 2009
Michael Ashton	2,044,293	56.67p	May 25, 2004	May 25, 2009

The aggregate number of ordinary shares underlying all of the outstanding options as of June 24, 2004 was 51,155,585. Such options have exercise prices ranging between 44.8 pence and 93 pence and expire between April 29, 2006 and September 26, 2013.

However it is the current intention of the Company that it will no longer grant options under any of the above option schemes to employees in view of the dilution caused by issuing shares under the schemes and the impact of the charge to the Company's profit and loss account.

**Deferred Share Bonus Plan**

Approximately 25 senior executives (including Executive Directors) participate in the Deferred Share Bonus Plan. Eligible participants are any employees of the Company selected by the

Remuneration Committee ("Eligible Employees"), or a trustee acting on behalf of such employees. The plan, which is operated by the Remuneration Committee, is designed to align the interests of participants with those of the shareholders by encouraging executives to build up and maintain shareholdings which are meaningful in the context of their remuneration.

Under the Deferred Share Bonus Plan, an Eligible Employee is required to defer no less than 50% of his or her bonus and to use the deferred portion to acquire shares in the Company ("Executive Shares"). The Company, in turn, issues to each Eligible Employee one Matching Share for each Executive Share so acquired. In addition to Matching Shares, the Remuneration Committee may award additional deferred shares to Eligible Employees ("Long-Term Incentive Plan Awards", or "LTIP Awards").

It is the current intention of the Remuneration Committee that the maximum value of an Eligible Employee's Matching Shares and LTIP Award will not exceed 100% of an employee's salary and bonus after the deduction of tax. LTIP Awards were made on May 5, 2004 to 21 participants at a share price of 59.92 pence, including awards of 700,534 shares to the Chief Executive Officer and 392,857 shares to the Finance Director. The maximum value which was awarded was 100% of the relevant participant's salary. No other LTIP Awards have previously been awarded under the Deferred Share Bonus Plan.

Matching Shares and LTIP Awards granted under the Deferred Share Bonus Plan are released to the relevant employee after three years provided certain conditions have been satisfied.

For Matching Shares issued prior to 2004, the relevant employee must remain in employment with the Company and the underlying Executive Shares must not have been sold. For Matching Shares issued in 2004, the Remuneration Committee has proposed the additional requirement that shares should be released only if certain performance conditions have been satisfied. Under this proposal, Matching Shares issued in 2004 will only be released if the total shareholder return of the Company is at or above the median of a specified comparator group of the Company's competitors.

In addition, the Remuneration Committee will be required to ensure that the underlying financial performance of the Company is consistent with its total shareholder return performance, by considering the Company's performance against financial measures such as turnover, profitability and cash flow. For example, no Matching Shares will be provided at the end of the holding period unless the Company is in profit.

For LTIP Awards, the relevant employee must remain in employment with the Company and certain performance conditions must be satisfied. The principal performance condition for the release of an LTIP Award is measured in terms of the total shareholder return of the Company relative to a comparator group. In addition, the Remuneration Committee will be required to ensure that the underlying financial performance of the Company is consistent with its total shareholder return performance, by considering the Company's performance against financial measures such as turnover, profitability and cash flow.

Participants have no rights to vote or receive dividends in respect of the shares awarded to an employee under the Deferred Share Bonus Plan prior to release.

The Company may issue 10% of its shares within a ten year period to satisfy share awards to employees under the Deferred Share Bonus Plan and any other share scheme operated by the Company under which shares are issued. No more than 5% of the Company's shares will be issued under the Deferred Share Bonus Plan or any other share scheme operated by the Company where shares are issued for executives provided that this limit may be exceeded if the executives are required to satisfy more stretching performance requirements. The Remuneration Committee will be monitoring the issue of shares during the ten-year period.

Shares subscribed will not rank for dividends payable by reference to a record date falling before the date on which the shares are acquired but will otherwise rank *pari passu* with existing shares. Application will be made to the relevant exchange on which the shares are listed for

admission to trading on the relevant exchange for new shares that are to be issued following the release of Matching Shares or an LTIP Award.

Matching Share awards are not transferable and will lapse if the participant attempts to effect a transfer. If a participant disposes of his Executive Shares during the holding period or leaves employment prior to the expiration of the holding period the Matching Share award will lapse unless the Remuneration Committee in its absolute discretion determines otherwise. In the event of a takeover, reconstruction, amalgamation or winding up of the Company then all Matching Share awards will be released unless in certain circumstances they are exchanged for Matching Share awards over shares in the acquiring company. In the event of a merger or demerger of the Company, the Committee may determine that all Matching Share awards will be released or the number of shares comprised in a Matching Share award may be adjusted.

LTIP Awards are not transferable and will lapse if the participant attempts to effect a transfer. If a participant leaves employment prior to the expiration of the vesting period, then the LTIP Award will lapse. However, on cessation for injury, disability, redundancy, retirement, death or other reasons at the absolute discretion of the Remuneration Committee, there may be proportionate release of LTIP Awards depending upon the lapse of time and the satisfaction of the attached performance conditions. In the event of a takeover, reconstruction, amalgamation, winding up, merger or de-merger of the Company then there may be proportionate release of LTIP Awards depending upon the satisfaction of the performance conditions at the point of the transaction. In addition, the Remuneration Committee shall take into account the amount of time elapsed since the date of grant of the LTIP Award in determining the proportion of the LTIP Award that shall be released.

On a variation of the capital of the Company, the number of shares awarded to an employee under the Deferred Share Bonus Plan may be adjusted in such manner as the Remuneration Committee determines and a professional advisor of the Company confirms to be fair and reasonable.

The Committee may not grant Matching Shares or LTIP Awards under the Deferred Share Bonus Plan more than five years after its adoption unless the Deferred Share Bonus Plan is extended pursuant to shareholder authority for a further period of up to five years.

Amendments to the rules may be made at the discretion of the Committee. However, the provisions governing eligibility requirements, equity dilution, share utilization and individual participation limits and the adjustments that may be made following a rights issue or any other variation of capital and the limitations on the number of shares that may be issued cannot be altered to the advantage of participants without prior shareholder approval, except for minor amendments to benefit the administration of the Deferred Share Bonus Plan, to take account of a change in legislation or to obtain or maintain favorable tax, exchange control or regulatory treatment for participants or for the Company and any subsidiary.

Shares acquired, awards and any other rights granted pursuant to the Deferred Share Bonus Plan are non-pensionable.

The Company has the ability to use new issue shares under the Deferred Share Bonus Plan. Any shares issued under this Deferred Share Bonus Plan would be subject to the limits set out above for the Option Schemes (i.e., the shares issued under this Deferred Share Bonus Plan would be aggregated with the shares issued under the Option Schemes when calculating the number of shares issued against the limits).

#### **Share Purchase Plan**

The Company's intention is to encourage share ownership at all levels of the business, thereby aligning all employees' interests with those of the shareholders. Accordingly, the Company introduced the SkyePharma International Share Purchase Plan ("the Employee Plan") and the Employee Stock Purchase Plan in February 2002.

All employees (including all the Executive Directors) are eligible to participate in the Employee Plan under the arrangements introduced in their respective countries.

The Employee Plan complements the Option Schemes as it is more focused on employee retention and enables the same remuneration policy applied to executives under the Deferred Share Bonus Plan to be applied to all employee levels, i.e., awarding matching shares on the basis of the number of employee purchased shares.

Under the Employee Plan, employees are given the opportunity to purchase Company shares up to a maximum of £1,500 per year (or local currency equivalent). The Company will then match each share purchased with an award of one ordinary share (each a "Matching Share"). The maximum ratio of Matching Shares to employee purchased shares is two to one although the current ratio adopted by the Company is one Matching Share for each share purchased. The Matching Shares are subject to a three-year holding period. Normally, the Matching Shares will only be released at the end of this holding period if the corresponding employee purchased shares have not been sold and the employee is still in employment at that time. Awards under this Employee Plan lapse if the holder is adjudicated bankrupt or when the holder sells his or her shares or ceases to be in the Company's employment during the restricted period determined by the Directors. Matching Shares cannot be released later than ten years after the date of the purchase of the shares.

The shares required for the Employee Plan are currently being purchased in the market rather than being issued by the Company. The Company does, however, want to have the flexibility to issue new shares for the purposes of the Employee Plan if this becomes necessary or desirable in the future and hence shareholder approval was obtained for this amendment to the Employee Plan at the Company's Annual General Meeting held on May 30, 2002.

## **Warrants**

### *'D' and 'E' Warrants*

The Company has issued warrants to Paul Capital giving rights to subscribe for 5 million SkyePharma ordinary shares at an exercise price of 73.75 pence, representing a 25% premium to the average trading price for the five trading days immediately prior to the closing date. At June 24, 2004, should the warrants be converted, they represented 0.8% of the Company's ordinary share capital. The warrants are divided into 2,500,000 Series D and 2,500,000 Series E warrants. The terms are identical save for the exercise dates. The Series D Warrants can be exercised at any time from the date of creation of the warrants until December 31, 2008 and the Series E Warrants can be exercised at any time from June 30, 2002 until December 31, 2008. There are standard provisions in the deed polls creating the warrants relating to provision for adjustment of the warrant rights in certain circumstances such as a capital reorganisation and relating to certain restrictions on the Company such as capital distributions and there are a number of provisions in the deed polls designed to comply with the Securities Act of 1933.

### *'F' Warrants*

The Company issued 'F' Warrants in December 2003 as part of the \$5 million loan with GE Capital Corp. The 'F' Warrants entitle the holders to subscribe for a total of 300,000 Ordinary Shares at any time until the repayment date of the loan at an exercise price of £1.20 per ordinary share.

### *Other Warrants*

Warrants were issued to former DepoTech shareholders by the Company in December 1999 as part of the acquisition of DepoTech. These warrants entitle their holders to subscribe for 291,777 ordinary shares at any time during the period beginning December 31, 1999 and ending on February 25, 2005 at an exercise price of \$1.453 per ordinary share.

**Item 7: Major Shareholders and Related Party Transactions****MAJOR SHAREHOLDERS**

As far as the Company is aware, it is neither directly nor indirectly owned or controlled by another corporation or any government, and there are no arrangements in place the operation of which may result in a change in its control.

As of June 24, 2004, the Company had notice or was aware that the following persons owned more than 3% of the outstanding ordinary shares:

	<b>Number of Ordinary Shares</b>	<b>% Holding</b>
Fidelity Investments	87,676,918	14.1
Dr Jacques Gonella	41,991,292	6.7
Standard Life Investments	24,350,019	3.9
Kowa Company Limited	30,000,000	4.8
Legal & General Investment Management Limited	21,740,453	3.5

The Company's major shareholders do not have different voting rights, except for Kowa's right to appoint a Non-executive Director pursuant to its investment agreement with the Company in May 2002.

Dr Jacques Gonella also has an interest in 12 million 'B' Deferred Shares which do not confer upon the holder the right to receive notice of or attend or vote at any general meeting of the Company. The Deferred Shares automatically convert into ordinary shares on the occurrence of certain events. The contingencies determining the conversion of the Deferred Shares into ordinary shares are set out in Note 22 of the Notes to SkyePharma's Consolidated Financial Statements included in Item 18 of this Form 20-F.

As of June 24, 2004, there were 18,588 holders of record of ordinary shares and 42 of such holders were beneficial U.S. holders representing 12% of the ordinary shares. In addition, at June 24, 2004 there were 138 holders of record of American Depositary Shares ("ADSs") representing 7% of the ordinary shares.

**RELATED PARTY TRANSACTIONS****Certain Arrangements in Respect of the Jago Acquisition**

On July 20, 2000, the following shares were issued to Dr Jacques Gonella, the vendor of Jago, under the Settlement Agreement that established full and final settlement of the deferred consideration payable on the acquisition of Jago:

- (i) 6 million ordinary shares;
- (ii) 12 million 'A' Deferred Shares which automatically converted into 12 million ordinary shares in April 2003, following the first commercial sale by GlaxoSmithKline of Paxil CR ; and
- (iii) 12 million 'B' Deferred Shares which will automatically convert into 12 million ordinary shares on the Company's receipt of a royalty statement under the current License Agreement with GlaxoSmithKline stating that reported sales of Paxil CR have exceeded (a) \$1,000 million during any calendar year prior to January 1, 2006 or (b) exceeded \$337 million between January 1, 2006 and May 3, 2006.

In the event that this third condition set out above is not satisfied prior to May 3, 2006, the Deferred 'B' Shares will not be converted and will be cancelled. The vendor shall not be entitled to any other compensation nor additional compensation.

On issue, the ordinary shares were recorded as share capital and share premium at a price of 94.25 pence. The Deferred Shares were recorded within non-equity share capital and non-equity share premium at a price of 94.25 pence, the fair value of those shares, on July 20, 2000.





### **Certain Arrangements in Respect of the Krypton Acquisition**

On January 8, 1996 the Company acquired Krypton from a series of trusts in which Ian Gowrie-Smith had an interest. The deferred consideration on the acquisition of Krypton provides that a maximum of 37.5 million ordinary shares would be issued contingent on a change in control of the Company at a share price of not less than 80 pence compounded at an annual rate of 10% (£1.71 as at December 31, 2003), or satisfaction of various conditions and hurdles which lapsed on December 31, 2003. No provision for deferred consideration had been recognized as at December 31, 2003.

### **Other Arrangements**

At the end of December 1998, Ian Gowrie-Smith (through a family-owned trust) acquired a 50% interest in 10 East 63<sup>rd</sup> Street Inc., the company which owns 10 East 63<sup>rd</sup> Street, a property in New York. In December 2002, Mr. Gowrie-Smith acquired the remaining 50% interest. SkyePharma PLC has been in occupation of that property since January 1997, subject to tenancy agreements based upon independent valuation. In August 2003, the Company took occupation of the entire building under an eight year tenancy agreement, at which time the annual rent was increased from \$420,000 per annum to \$720,000 per annum until August 2008, and \$943,000 per annum from August 2008 to August 2011. The Company intends to sub-lease part of the premises and is actively seeking tenants.

In December 2001, the Company entered into several agreements with Astralis Limited concerning the development of a novel injectable vaccine therapy for the treatment of all forms of psoriasis, a chronic skin disorder. In a separate transaction, the Company made a total equity investment in Astralis of \$20 million in convertible preferred shares. In January 2004 SkyePharma converted all of its convertible preferred shares of Astralis into common stock of Astralis. The resulting holding represents approximately 35.7% of the common shares. Michael Ashton, the Company's Chief Executive Officer, was appointed to the Astralis Board in January 2002. Astralis is not regarded as an associated undertaking for accounting purposes as the Directors have concluded that the Group does not exert significant influence. For further details of the Astralis transactions see "Item 4: Information on the Company Business Operations Collaborative Arrangements Other Collaborative Arrangements".

In December 2001, the Company entered into several agreements with e-nutriceuticals inc, as a result of which the Company acquired 1 million convertible preference shares in e-nutriceuticals. In August 2003, e-nutriceuticals merged with Vital Living Inc. and as a result of the merger SkyePharma acquired 14,204,548 common shares in Vital Living. During the year, the Group acquired 1 million series D convertible preferred shares, \$1 million of 12% senior secured convertible notes due 2008 and 1 million warrants expiring 2008 of Vital Living for £1.2 million (\$2.0 million). As at December 31, 2003, the total SkyePharma holding was 14,204,548 common shares, 1 million series D convertible preferred shares, \$1 million 12% senior secured convertible notes due 2008 and 1 million warrants expiring 2008, representing approximately 24.4% of the ordinary share capital. (28.1% assuming conversion of the preferred shares, notes and warrants). Michael Ashton, the Company's Chief Executive Officer, was appointed to the Vital Living Board in January 2004. Vital Living is not regarded as an associated undertaking for accounting purposes as the Directors have concluded that the Group does not exercise significant influence over Vital Living.

In 2003, the Company entered into several agreements with Micap plc concerning the application of micro-encapsulation technology to drug delivery. The Company subscribed for 2,500,000 Ordinary Shares at a price of 80 pence as part of a fundraising of 3,125,000 Ordinary Shares approved by Micap's shareholders at an Extraordinary General Meeting on January 13, 2003. The remaining 625,000 Ordinary Shares were subscribed for by the Sigma Technology Venture Fund, an existing shareholder. In 2003 Micap undertook an initial public offering and as part of the renegotiation of Micap in conjunction with the offering, the Company's shareholding was

converted into 5,238,334 ordinary shares, representing approximately 18.2% of the ordinary share capital, and 1,830,000 convertible shares. Ian Gowrie-Smith, the Company's was appointed to the Micap Board in January 2003.

During 2003, SkyePharma investigated the pharmaceutical applications of Micap's micro-encapsulation technology, in the areas of oral and topical drug delivery. The Company was paid for its services. In March 2004, the Company exercised an option granted to it under one of its agreements with Micap to complete a technology access and license agreement with Micap that allows the Company to use Micap's encapsulation technology in up to ten nominated pharmaceutical products to be selected by SkyePharma.

## **Item 8: Financial Information**

### **CONSOLIDATED STATEMENTS AND OTHER FINANCIAL INFORMATION**

See "Item 18: Financial Statements".

### **LEGAL PROCEEDINGS**

Save as disclosed below, the Company and its subsidiaries are not involved in any legal or arbitration proceedings which are expected to have, or have had in the past twelve months preceeding the date of this document, a significant impact on the Company.

On April 12, 2002, a Class Action Complaint was filed by the Action Alliance of Senior Citizens of Greater Philadelphia, a non-profit Pennsylvania corporation, individually and on behalf of all others similarly situated, against Elan Corporaton PLC and SkyePharma Inc. The action was filed in the U.S. District Court for the Eastern District of Pennsylvania. On May 15, 2002, a second Class Action Complaint was filed in the same court by Jeanine Weber, and on June 12, 2002, a third Class Action Complaint was filed in the same court by Charles Frederick. On October 14, 2002, a Consolidated Class Action Complaint (the "Consolidated Complaint") was filed, covering all three cases, and on the same date the plaintiffs filed a motion requesting class certification. The Consolidated Complaint is brought under the Sherman Anti-trust Act (the "Act") and various state statutes, and alleges a contract in restraint of trade as well as an attempt to monopolise the market for Naprelan in violation of those laws. The Consolidated Complaint seeks injunctive relief and damages, multiple damages, and restitution in unspecified amounts. On November 22, 2002, the case was stayed by agreement of the parties pending final resolution of certain patent litigation between Elan and Andrx that relates to Elan's patents covering Naprelan. The case remains stayed at the present time. The Company believes that the claims asserted in the Consolidated Complaint are without merit and will vigorously defend the action.

In late December 2002, SkyePharma, Inc. was served with a subpoena by the U.S. Federal Trade Commission ("FTC"), requesting documents relating to the same agreement between Elan and SkyePharma at issue in the Andrx lawsuit and the Pennsylvania class action litigation described above. SkyePharma, Inc. has cooperated with the FTC's request and produced documents and provided other information in response to the subpoena.

### **DIVIDEND POLICY**

The Company has not paid dividends in the last 10 years on its ordinary shares and does not intend to pay dividends in the foreseeable future. The Company currently intends to retain all of its earnings to finance its operations and future growth. Moreover, under current U.K. law, the Company's accumulated realized profits must exceed its accumulated realized losses (on a nonconsolidated basis) before dividends can be paid.

### **SIGNIFICANT CHANGES**

There have been no significant changes since the date of the Consolidated Financial Statements included in this Form 20-F.

**Item 9: The Offer and Listing****STOCK PRICE HISTORY**

The principal trading market for the ordinary shares is the London Stock Exchange (the "LSE").

The table below sets forth, for the periods indicated, the highest and lowest closing market quotations for the Company's ordinary shares as derived from the Daily Official List of the LSE and the highest and lowest sales prices of the Company's ADSs on The Nasdaq National Market. The mid-closing price for the ordinary shares on the LSE and the last sale price for the ADSs on The Nasdaq National Market on June 24, 2004 was 65.00 pence per ordinary share and \$11.93 per ADS. See "Exchange Rate Information" with respect to the exchange rates applicable to the periods set forth below.

	SkyePharma Ordinary Shares		SkyePharma ADSs	
	High	Low	High	Low
	(Pence per Company Ordinary Share)		(\$ per Company ADS)	
<b>Year ended December 31, 1999</b>	88.00	45.3	15.13	6.38
<b>Year ended December 31, 2000</b>	190.00	49.8	29.38	7.38
<b>Year ended December 31, 2001</b>	108.00	49.0	15.50	7.01
<b>Year ended December 31, 2002</b>	80.25	39.0	11.90	6.25
<b>Year ended December 31, 2003</b>	79.25	41.50	14.00	6.60
<b>Year ended December 31, 2002</b>				
First Quarter	74.00	52.50	10.85	7.45
Second Quarter	80.25	62.75	11.90	9.03
Third Quarter	66.00	45.00	9.75	6.95
Fourth Quarter	52.00	39.00	8.94	6.25
<b>Year ended December, 2003</b>				
First Quarter	50.00	41.50	8.44	6.60
Second Quarter	73.00	45.75	12.99	7.30
Third Quarter	74.50	57.00	12.10	9.65
Fourth Quarter	79.25	57.00	14.00	9.62
<b>Year ended December 31, 2004</b>				
First Quarter	72.25	58.75	13.66	11.24
Second Quarter (through June 24, 2004)	69.75	50.50	13.30	9.09
<b>Monthly Data</b>				
December 2003	79.00	74.00	14.00	13.31
January 2004	70.75	66.00	13.66	12.20
February 2004	72.25	62.75	13.58	11.75
March 2004	65.50	58.75	12.05	11.24
April 2004	69.75	61.25	13.30	10.20
May 2004	64.50	50.50	11.82	9.09
June 2004 (through June 24, 2004)	65.50	59.50	12.07	11.00

**STOCK EXCHANGES ON WHICH THE COMPANY'S SHARES ARE LISTED**

The ordinary shares were admitted to the Official List of the LSE on May 3, 1996 and are quoted under the symbol "SKP". Prior to that time, the ordinary shares traded on the LSE's Alternative Investment Market, from January 9, 1996 to May 2, 1996, and on the LSE's Unlisted Securities Market, from October 26, 1987 to January 8, 1996.

The LSE classifies equity securities based on 12 levels of normal market size, ranging from 200,000 to 500 shares. These levels of normal market size reflect the turnover by value in each of the Company's shares over the past 12 months. The ordinary shares have a normal market size of 10,000 shares. The normal market size classification for each equity security is subject to quarterly review in the light of trading volumes in the previous quarter and to adjustment, as appropriate. U.K. market makers are normally required to make a two-way market in sizes of not less than the normal market size and to report all transactions to the LSE within three minutes. In respect of securities with a normal market size greater than 2,000, transactions of not more than three times normal market size are published immediately as to size and price, but transactions in excess of three times normal market size are not published until after 60 minutes.

The Company's ADSs are quoted on The Nasdaq National Market under the symbol "SKYE". ADSs are issued by the Bank of New York as depositary under the Deposit Agreement dated as of July 8, 1998. Each ADS represents ten ordinary shares.

**Item 10: Additional Information**

**MEMORANDUM AND ARTICLES OF ASSOCIATION**

The following summarizes certain provisions of SkyePharma PLC's Memorandum and Articles of Association and applicable English law. The summary is qualified in its entirety by reference to the UK Companies Act and SkyePharma's Memorandum and Articles of Association. Investors can obtain copies of the Memorandum and Articles of Association by contacting the Company Secretary at the registered office of the Company. On May 30, 2002 the Company adopted new Articles of Association.

**Objects and Purposes**

The Company was incorporated in England and Wales on March 10, 1910 under the Companies Act 1908 as a Company limited by shares and was re-registered in 1982 as a public limited company under the Companies Act 1948 to 1980. The Company is registered under company number 107582. The Company was re-registered as SkyePharma PLC on January 8, 1996.

The objects of the Company are set out in full in clause 4 of its memorandum of association which provides, among other things, that the Company's objects are to carry on in any part of the world any business which, in the opinion of the directors, may seem conveniently carried on in connection with or ancillary to any of several diverse businesses, including applying for, purchasing or otherwise acquiring and holding, using, developing, selling, licensing or otherwise disposing of or dealing with patents, copyrights, designs, trade marks, secret processes, know-how and inventions and any interest therein.

**Directors**

The business and affairs of the Company shall be managed by the directors.

A director may not vote or count towards the quorum on any resolution concerning any proposal in which he (or any connected person) to his knowledge has a material interest (other than by virtue of his interest in securities of the Company), which includes the voting of

compensation awards to themselves. This prohibition does not apply to any of the following matters:

- (i) a contract or arrangement for giving to the director security or as guarantee or indemnity in respect of
  - a) money lent by him or obligations undertaken by him or by any other person at the request of or for the benefit of the Company or any of its subsidiaries; or
  - b) a debt or obligation of the Company or any of its subsidiaries for which he himself has assumed responsibility in whole or part under a guarantee or indemnity or by the giving of security.
- (ii) where the Company or any of its subsidiary undertakings is offering securities in which offer the director is, or may be, entitled to participate as a holder of securities or in the underwriting or sub underwriting of which the director is to participate;
- (iii) relating to another company in which he and any persons connected to him do not to his knowledge hold an interest in shares representing 1 per cent or more of any class of the equity share capital or of the voting rights in that company;
- (iv) relating to a pension, superannuation or similar scheme or retirement, death or disability benefits scheme or employees' share scheme which has been approved by the inland revenue or is conditional upon that approval or does not award him any privilege or benefit not awarded to the employees to whom the scheme relates; or
- (v) concerning insurance which the Company proposes to maintain or purchase for the benefit of persons including directors.

A director may not vote or be counted in the quorum on any resolution which concerns his or her own appointment with the Company or any other company in which the Company is interested.

The UK Companies Act requires a director of a company who is in any way interested in a contract or proposed contract with the Company to declare the nature of his interest at a meeting of the directors of the Company.

The directors may exercise all the powers of the Company to borrow money. The borrowing powers contained in the articles of association may only be varied by amending the articles of association.

A director must retire at the conclusion of the first annual general meeting after he reaches the age of 70 and thereafter annually, and being eligible, may stand for re-election.

A director is not required to hold an interest in the shares of the Company.

At each annual general meeting of the Company one-third of the directors for the time being (rounded down if necessary) are required to resign from office.

#### **Classes of Shares**

The authorized share capital of the Company is £111,400,000 divided into 1,090,000,000 ordinary shares of 10p each, 12,000,000 "A" Deferred Shares of 10p each (which have been converted into ordinary shares) and 12,000,000 "B" Deferred Shares of 10p each.

#### ***Provisions set out applying to the Ordinary Shares of 10p each***

- (a) Dividends

Under English law, dividends are payable on the Company's ordinary shares only out of profits available for distribution, as determined in accordance with accounting principles generally accepted in the UK and by the Companies Act 1985. The Company in general meeting may declare dividends by ordinary resolution, but such dividend may not exceed the amount recommended by

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

the directors. The directors may pay interim dividends if it appears they are justified by the Company's financial position.

Dividends unclaimed for 12 years after they become due for payment shall, unless the directors resolve otherwise, be forfeited and revert to the Company.

(b) Voting Rights

Every member who is present in person or represented at any general meeting of the Company and who is entitled to vote has one vote on a show of hands. On a poll every member who is present or represented has one vote for every share held.

Holders of ordinary shares may appoint a proxy, including a beneficial owner of those shares, to attend, speak and vote on their behalf at any shareholder's meeting.

If any sum remains unpaid in relation to a member's shareholding, that member is not entitled to vote that share unless the board otherwise determines.

(c) Rights to share in the Company's profits

The profits of the Company available for dividend and resolved to be distributed shall be applied in the payment of dividends (if any are declared) to members in accordance with their respective rights and priorities.

(d) Rights to share in any surplus in the event of liquidation

On a winding up of the Company, the balance of the assets available for distribution, after deduction of any provision made under the Companies Act 1985 and subject to any special rights attaching to any class of share, shall be applied in repaying to the members of the Company the amounts paid up on the shares held by them. Any surplus assets will belong to the holders of any ordinary shares then in issue according to the numbers of shares held by them.

(e) Redemption and sinking provisions

The Company may by special resolution create and sanction the issue of shares which are, or at the option of the Company or the holder are to be liable, to be redeemed, subject to and in accordance with the provisions of the Companies Act 1985. The special resolution sanctioning the issue shall also make such alterations to the articles of the Company as are necessary to specify the terms on which and the manner in which the shares are to be redeemed. The Company has no redeemable shares in issue and there are no provisions relating to sinking funds in the articles of the Company. The Company has not established a sinking fund.

(f) Liability to further capital calls by the Company.

The directors may make calls upon the members in respect of any monies unpaid on their shares. Each member shall pay to the Company at the time and place specified the amount called on his shares. A call may be revoked or postponed as the directors determine.

(g) Substantial shareholders

There are no provisions contained in the articles of the Company which discriminate against any existing or prospective holder of securities as a result of such shareholder owning a substantial number of shares.

### *Provisions set out applying to the "B" Deferred Shares*

The "B" Deferred Shares do not confer any right to participate in any profits of the Company or to receive notice of or attend any general meeting of the Company. Each "B" Deferred Share will be redesignated as an ordinary share on the first occasion that total reported sales of Geomatrix versions of Paroxetine/Paxil exceed \$1 billion in any calendar year ending prior to January 1, 2006 or, if that does not happen, then if such sales exceed \$337 million in the period January 1, 2006 to May 3, 2006.





The right of redesignation attaching to the "B" Deferred Shares will lapse if this event has not taken place by May 3, 2006.

#### **Variation of rights**

Whenever the capital of the Company is divided into different classes of shares, the special rights attached to any class of shares may be modified either with the consent in writing of the holders of three quarters of the issued shares of the class or with the sanction of an extraordinary resolution passed at a separate general meeting of the holders.

#### **Shareholders' Meetings and Notices**

The Company is required to hold a general meeting each year as its annual general meeting in addition to other meetings (called extraordinary general meetings) as the directors think fit. The type of meeting will be specified in the notice calling it. Not more than 15 months may elapse between the date of one annual general meeting and the next.

In the case of an annual general meeting or the meeting for the passing of a special resolution (requiring the consent of a 75% majority), 21 clear days' notice is required. In other cases, 14 clear days' notice is required. The notice must specify the place, the date, and the hour of the meeting, and the general nature of the business to be transacted.

#### **Limitations on foreign shareholders**

There are no limitations imposed by English law or the Company's Memorandum or Articles of Association on the right of non-residents or foreign persons to hold or vote the Company's ordinary shares other than the limitations that would generally apply to all of the Company's shareholders.

#### **Change of Control**

There are no provisions in the Articles of Association that would have an effect of delaying, deferring or preventing a change in control of the Company and that would operate only with respect to a merger, acquisition or corporate restructuring involving the Company or any of its subsidiaries.

#### **Disclosure of Interests in Shares**

The UK Companies Act gives the Company the power to require persons whom it believes to have, or to have acquired in the previous three years, an interest in its voting shares to disclose certain information with respect to those interests. Failure to supply the information required may lead to disenfranchisement of the relevant shares and a prohibition on their transfer and receipt of dividends and other payments in respect of those shares. In this context the term "interest" is widely defined and will generally include an interest of any kind whatsoever in voting shares, including an interest of a holder of SkyePharma ADSs. Disclosure of ownership is covered by the London Stock Exchange Regulations and the Companies Act. Shareholders holding beneficial interests in excess of 3% are required to disclose this interest.

#### **MATERIAL CONTRACTS**

At March 31, 2000, a Settlement Agreement was signed establishing the full and final settlement of the deferred consideration payable to the vendor of Jago, Dr. Gonella. The settlement was approved by shareholders at the Company's Annual General Meeting held on July 11, 2000 to be made entirely in shares. On July 20, 2000, 6 million ordinary shares were issued to Dr. Gonella at a price of 94.25 pence. Also on July 20, 2000, 12 million "A" and 12 million "B" non-equity Deferred Shares were issued. The contingencies determining the conversion of the Deferred Shares into ordinary shares are set out in Note 22 of the Notes to SkyePharma's Consolidated Financial Statements included in Item 18 of this Form 20-F. Following the April 2002 U.S. launch of Paxil CR

by GlaxoSmithKline and the first commercial sale of Paxil, Dr. Gonella's 12 million "A" Deferred Shares have been converted into 12 million ordinary shares. In the event that the remaining conditions are not satisfied prior to May 3, 2006, the "B" Deferred Shares will not be converted and will be cancelled. The vendor will not be entitled to any other compensation nor additional compensation. On issue, the ordinary and Deferred Shares were recorded in share capital and share premium. At December 31, 1999 prior to the issue of shares, in the Directors' opinion, 30 million ordinary shares were likely to be issued under the terms of the Settlement Agreement and a figure of £33 million was recorded within shares and warrants to be issued, based upon a closing share price of 110 pence on March 31, 2000, the date of the Settlement Agreement.

In December 2002, the Company entered into a development and commercialization agreement under which Endo Pharmaceuticals Inc. received an exclusive license to the U.S. and Canadian marketing and distribution rights for two of the Company's patented development products, DepoDur, an injectable product, and Propofol IDD-D, a product using the Company's IDD solubilization technology, with options to negotiate for other development products in the area of pain management. In return, the Company received a \$25 million payment on signing in respect of DepoDur. In addition, the Company may receive further milestone payments totaling \$95 million. This amount comprises total milestone payments of \$10 million for DepoDur through FDA approval, a \$15 million milestone payment when net sales of DepoDur reach \$125 million in a calendar year, and a \$20 million milestone payment when net sales of DepoDur reach \$175 million in a calendar year. In addition, the amount comprises total milestone payments of \$50 million for Propofol IDD-D. The Propofol IDD-D milestone payments are payable when the product successfully achieves certain regulatory milestones, including FDA approval, except that, in the event the FDA-approved labeling fails to meet the parties' target labeling, only \$10 million becomes payable upon FDA approval, with the remaining \$40 million being due upon the achievement of certain sales targets. The Company will also receive a share of each product's sales revenue that will increase from 20% to a maximum of 60% of net sales as the products' combined sales achieve certain thresholds in any given year. The agreement provides for the parties to work together and complete the necessary clinical, regulatory and manufacturing work for regulatory approval of DepoDur and Propofol IDD-D in the United States and Canada. The Company will be primarily responsible for clinical development up to final FDA approval and for product manufacture, including all associated costs. Upon approval, Endo will market each product in the United States and Canada with the Company as supplier. In respect of the first product launched under the agreement, the Company will pay Endo a fixed contribution in relation to marketing activities undertaken by Endo in respect of the first and second year of commercialization. Endo will be responsible for funding and conducting any post-marketing studies and for selling and marketing expenses. The agreement expires with respect to each product upon the later of the expiry of all relevant patents and the 15th anniversary of the date of first commercialization. The agreement may be terminated in various cases, including by Endo in the event the Company experiences delays in obtaining regulatory approval for the products or fails to achieve the target labeling and, without cause, upon sixty days' notice provided that, in such an event, Endo shall pay an undisclosed termination fee to the Company.

In March 2000, the Company entered into an agreement with Bioglan for the manufacture, marketing and distribution of Solaraze® in Europe for an upfront licensing fee and royalty payments. In December 2000, the Company entered into a further agreement with Bioglan for the license of marketing rights to the United States, Canada and Mexico for Solaraze®, for which Bioglan paid a \$14 million fee and agreed to pay further significant milestone payments upon the commercialization of Solaraze®. On May 13, 2000, the Company announced that it had agreed to transfer all rights to market Solaraze® in Europe to Shire for total consideration of up to £15 million. Of this amount, £2.1 million is contingent on various conditions, including Solaraze®'s launch in certain European countries. In addition, SkyePharma will receive royalties on all European sales from Shire. In addition, the Company agreed to pay the administrators an amount of £0.7 million. For more details on the history of these agreements, see "Item 4: Information on the Company Business Operations Drug Delivery Platforms Topical Approved Topical Products Solaraze®."

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

In March 1996, the Company entered into a License Agreement with SmithKline Beecham (now part of GlaxoSmithKline) for the development, manufacture and marketing of a modified release version of Paxil/Seroxat (paroxetine HCL) using a combination of the Positioned Release and Zero Order Geomatrix systems, known as Paxil CR. Paxil is an FDA-approved drug that is currently marketed primarily in the United States and Europe and is an immediate release formulation prescribed for central nervous system disorders. Paxil CR was filed with the FDA by SmithKline Beecham in December 1997 and approved by the FDA in February 1999 for the 12.5 and 25mg dosage forms. Subsequently Paxil CR has been approved for four additional indications: panic disorder, the continuous treatment of PMDD, social anxiety disorder and the intermittent treatment of PMDD.

Under the terms of the License Agreement with SmithKlineBeecham, the Company will receive royalty payments on net sales of Paxil CR until certain patents have expired. The Company has received such payments since its launch in April 2002. The Company is entitled to an increased royalty rate in any country or territory in which certain GlaxoSmithKline patents have expired and in which Jagotec AG owns a patent which contains an existing, valid and enforceable claim that prevents a third party from commercializing a delivery system for paroxetine based on or using the Geomatrix technologies. In January 2004, the Company announced that it was in discussion with GlaxoSmithKline over the royalty rate received on sales of Paxil CR. SkyePharma believes, based on the contract and external legal advice, that it has been entitled to the increased royalty rate from September 8, 2003, the date of entry of generic paroxetine in the U.S. market. This position has been disputed by GlaxoSmithKline. If the Company is unable to reach agreement on this issue based on discussions with GlaxoSmithKline, the dispute will go to arbitration, as provided under the contract. For a copy of the License Agreement see Exhibit 4.6 to this Form 20-F.

For a description of transactions with related parties, see "Item 7: Major Shareholders and Related Party Transactions".

### EXCHANGE CONTROLS

There are currently no limitations, either under the laws of the United Kingdom or in the Articles of Association of the Company, on the rights of non-residents to hold, or to vote on Ordinary Shares. Additionally, there are currently no United Kingdom foreign exchange control restrictions on the conduct of the Company's operations or affecting the remittance of dividends on unrestricted shareholders' equity.

### TAXATION

The following is a summary of the material U.S. federal income and the United Kingdom tax consequences of owning and disposing of ordinary shares or ADSs of the Company by a U.S. Holder as defined below and a Non-U.S. Holder that holds the ordinary shares or ADSs as capital assets.

This summary is not exhaustive of all possible tax considerations and does not take into account the specific circumstances of any particular investors (such as tax-exempt organizations, life insurance companies, dealers in securities and currencies, traders in securities that elect to use a mark-to-market method of accounting, investors liable for alternative minimum tax, investors that actually or constructively own 10% or more of the voting stock of the Company, investors that hold ordinary shares or ADSs as part of a straddle or a hedging or conversion transaction, holders who acquired the stock units or ADS as compensation, or investors whose functional currency is not the U.S. dollar) that may be subject to special rules. In addition to these classes of holders, for United Kingdom tax purposes, special rules may apply also to holders that are banks, regulated investment companies or other financial institutions.

This summary is based on the tax laws of the United States (including the Internal Revenue Code of 1986, as amended, its legislative history, existing and proposed regulations, published rulings and court decisions) and on the tax laws of the United Kingdom all as in effect on the date

hereof, as well as on the Convention Between the Government of the United States of America and the Government of the United Kingdom of Great Britain and Northern Ireland for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with respect to Taxes on Income and Capital Gains entered into force April 25, 1980 (the "Old Treaty") and entered into force on March 31, 2003 (the "New Treaty"), as well as the Convention between the Government of the United States and the Government of the United Kingdom of Great Britain and Northern Ireland for the Avoidance of Double Taxation and Prevention of Fiscal Evasion with respect to Taxes on Estates of Deceased Persons and on Gifts as in effect on the date hereof (the "Estate Tax Treaty"). These laws are subject to change (or changes in interpretation), possibly with retroactive effect.

The New Treaty is effective in respect of taxes withheld at source for amounts paid or credited on or after May 1, 2003. Other provisions of the New Treaty, however, took effect on January 1, 2004. The rules of the Old Treaty will remain applicable until these effective dates. A U.S. Holder who is eligible for the benefits of the Old Treaty and New Treaty, however, may, in certain circumstances, elect to have the Old Treaty apply in its entirety for a period of twelve months after the applicable effective dates of the New Treaty. Holders of ordinary shares or ADSs are advised to consult their own tax advisers with respect to the overall tax implications of the New Treaty, including the implications of making the election.

In addition, this summary is based in part upon the representations of the Depositary and the assumption that each obligation in the Deposit Agreement and any related agreement will be performed in accordance with their respective terms.

For purposes of this discussion, a "U.S. Holder" is any beneficial owner of ordinary shares or ADSs that is for United States federal income tax purposes:

- (1) a citizen or resident of the United States;
- (2) a United States domestic corporation;
- (3) an estate the income of which is subject to United States federal income tax without regard to its source; or
- (4) a trust if a court within the United States is able to exercise primary supervision over the administration of the trust and one or more United States persons have the authority to control all substantial decisions of the trust.

The discussion does not address any aspects of United States taxation other than federal income taxation. In addition, the following summary of certain U.K. tax considerations does not address the tax consequences of owning and disposing the Company's ordinary shares or ADSs to a U.S. Holder:

- (1) that is resident (or, in the case of an individual, ordinarily resident) in the United Kingdom for U.K. tax purposes,
- (2) whose holding of ordinary shares or ADSs is effectively connected with a permanent establishment in the United Kingdom through which such U.S. Holder carries on business activities or, in the case of an individual who performs independent personal services, with a fixed base situated therein,
- (3) who is not otherwise eligible for benefits under the Treaty with respect to income and gain from the ordinary shares or ADSs.

***Prospective investors are urged to consult their own tax advisors regarding the United States federal, state and local and the United Kingdom and other tax consequences of acquiring, owning and disposing of ordinary shares and ADSs. In particular, a U.S. Holder should confirm with its advisor whether it is eligible for the benefits of the Old Treaty or New Treaty and should discuss the consequences of failing to be so eligible.***

In general, and taking into account the earlier assumptions, for United States federal income and United Kingdom income tax purposes, holders of ADRs evidencing ADSs will be treated as the beneficial owners of the ordinary shares represented by those ADSs. Exchange of ordinary shares for ADRs, and ADRs for ordinary shares, generally will not be subject to United States federal income tax or to United Kingdom income tax.

## **Taxation of Dividends**

### ***United Kingdom Taxation***

The taxation of dividends paid in respect of the ordinary shares depends upon the law and practice in force at the time dividends are paid. The following summary is based upon current law and practice, which may change by the time that any dividends become payable.

For dividends paid on or after April 6, 1999, under the Old Treaty an Eligible U.S. Holder is entitled to receive from the U.K. a tax credit ("Tax Credit Amount") in respect of any dividend received equal to one-ninth of the amount of the cash dividend. The payment is reduced by an amount equal to 15% of the sum of the dividend payment and the tax credit amount ("the 15% U.K. withholding tax"). The 15% U.K. withholding tax will not, however, exceed such amount and reduces the Tax Credit Amount to \$0.

Under the New Treaty, an eligible U.S. holder will not be entitled to a tax credit nor be subject to a withholding tax by the United Kingdom.

For the purposes of this document, the term "Eligible U.S. Holder" means a U.S. Holder that is a beneficial owner of an ordinary share or an ADS and the cash dividend paid with respect thereto and that

- (1) is an individual or a corporation resident in the United States for purposes of the Treaty (and, in the case of a corporation, is not also resident in the United Kingdom for U.K. tax purposes);
- (2) is not a corporation which, alone or together with one or more associated corporations, controls, directly or indirectly, 10% or more of the voting stock of the Company;
- (3) holds the ordinary share or ADS in a manner which is not effectively connected with a permanent establishment in the United Kingdom through which such U.S. Holder carries on business or with a fixed base in the United Kingdom from which such holder performs independent personal services;
- (4) under certain circumstances, is not an investment or holding company, 25% or more of the capital of which is owned, directly or indirectly by persons that are not individuals resident in, and are not nationals of, the United States;
- (5) under certain circumstances, is not exempt from federal income tax on dividend income in the United States; and
- (6) is eligible for benefits under the Treaty with respect to income and gain from the ordinary shares or ADS's.

An Eligible U.S. Holder may claim the Treaty Payment to which he is entitled from the Inland Revenue. However, under Rev. Proc. 2000-13 an Eligible U.S. Holder may elect to be treated as receiving the Tax Credit Amount due under the Treaty without affirmatively making a claim to the Inland Revenue. Please see a complete discussion of these rules below in the discussion of U.S. taxation.

While a claim for payment is no longer necessary, if a claim for payment is made, it must be made within 6 years of the U.K. year of assessment (generally, the 12 month period ending April 5 in each year) in which the related dividend was paid. The first such claim by an Eligible U.S. Holder for payment under these procedures is made by sending the appropriate U.K. forms in duplicate to

the Philadelphia Service Center, Foreign Certification Unit, P.O. Box 16347, DP535B, Philadelphia, PA 19114. If the Eligible U.S. Holder qualifies as a U.S. resident, the Internal Revenue Service will certify the form to that effect and forward it to the U.K. Inland Revenue. Forms may be obtained by writing to the U.S. Internal Revenue Service, Assistant Commissioner International, 950 L'Enfant Plaza South, S.W., Washington, D.C. 20024, Attention: Taxpayers Service Division. Because a refund claim is not considered made until the U.K. tax authorities receive the appropriate form from the Internal Revenue Service, forms should be sent to the Internal Revenue Service well before the end of the applicable limitation period. Any claim under these procedures after the first claim should be filed directly with the Inland Revenue International Centre for Non-Residents, P.O. Box 46, Nottingham NG2 1BD, England.

U.S. Holders who are not resident or ordinarily resident for tax purposes in the United Kingdom and have no other source of U.K. income are not required to file a U.K. income tax return.

### *United States Taxation*

Under the United States federal income tax laws, and subject to the passive foreign investment company rules discussed below, the gross amount of any dividend paid to a U.S. Holder by the Company out of its current or accumulated earnings and profits (as determined for United States federal income tax purposes) is subject to United States federal income taxation. Dividends paid to a non-corporate U.S. holder in taxable years beginning after December 31, 2002 and before January 1, 2009 that constitute qualified dividend income will be taxable to the holder at a maximum tax rate of 15% provided that the ordinary shares or ADSs are held for more than 60 days during the 120 day period beginning 60 days before the ex-dividend date and the holder meets other holding period requirements. The Internal Revenue Service recently announced that it will permit taxpayers to apply a proposed legislative change to this holding period requirement as if such change were already effective. This legislative "technical correction" would change the minimum required holding period, retroactive to January 1, 2003, to more than 60 days during the 121-day period beginning 60 days before the ex-dividend date. Dividends paid by the Company with respect to its ordinary shares or ADSs generally will be qualified dividend income.

U.S. Holders that are eligible for the benefits of the Old Treaty and have properly filed Internal Revenue Form 8833 may include any United Kingdom tax deemed withheld from the dividend payment in this gross amount even though they do not in fact receive it. Subject to certain limitations, the United Kingdom tax deemed withheld in accordance with the Old Treaty and paid over to the United Kingdom will be creditable against the U.S. Holder's United States federal income tax liability. In addition, special rules apply in determining the foreign tax credit limitation with respect to dividends that are subject to the maximum 15% rate. Under the New Treaty, a U.S. Holder will not be entitled to a United Kingdom tax refund, but also not be subject to United Kingdom withholding tax. In that case, the U.S. Holder therefore will include in income for United States federal income tax purposes only the amount of the dividend actually received, and the receipt of a dividend will not entitle the U.S. Holder to a foreign tax credit.

The dividend is taxable to the U.S. Holder when the holder, in the case of ordinary shares, or the Depositary, in the case of ADSs, receives the dividend, actually or constructively. The dividend will not be eligible for the dividends received deduction generally allowed to United States corporations in respect of dividends received from other United States corporations. The amount of the dividend distribution includible in income of a U.S. Holder will be the U.S. dollar value of the British pounds sterling payments made, determined at the spot British pound sterling/U.S. dollar rate on the date such dividend distribution is includible in the income of the U.S. Holder, regardless of whether the payment is in fact converted into U.S. dollars. Generally, any gain or loss resulting from currency exchange fluctuations during the period from the date the dividend payment is includible in income to the date such payment is converted into U.S. dollars will be treated as ordinary income or loss and will not be eligible for the special tax rate applicable to qualified dividend income. Such gain or loss will generally be from sources within the United States for foreign tax credit limitation purposes. Distributions in excess of current and accumulated earnings

and profits, as determined for United States federal income tax purposes, will be treated as a return of capital to the extent of the U.S. Holder's basis in the ordinary shares or ADSs and thereafter as capital gain.

Dividends will be income from sources outside the United States, but generally will be "passive income" or, in the case of certain holders, "financial services income" which is treated separately from other types of income for foreign tax credit limitation purposes.

## **Taxation of Capital Gains**

### ***United Kingdom Taxation***

U.S. Holders who are not resident or (in the case of individuals only) ordinarily resident for tax purposes in the United Kingdom will not be liable for U.K. tax on capital gains realized on the disposal of their ADSs or ordinary shares unless such ADSs or ordinary shares are used, held or acquired for the purposes of a trade, profession or vocation carried on in the United Kingdom through a branch or agency.

### ***United States Taxation***

Under the United States federal income tax laws, and subject to the passive foreign investment company rules discussed below, upon a sale or other disposition of ordinary shares or ADSs, a U.S. Holder will recognize gain or loss for United States federal income tax purposes in an amount equal to the difference between the U.S. dollar value of the amount realized and the U.S. Holder's tax basis (determined in U.S. dollars) in such ordinary shares or ADSs. Generally, such gain or loss will be long-term capital gain or loss if the U.S. Holder's holding period for such ordinary shares or ADSs exceeds one year, and will be from sources within the United States for foreign tax credit limitation purposes. Long-term capital gain of a non-corporate U.S. Holder that is recognized on or after May 6, 2003 and before January 1, 2009 is taxed at a maximum rate of 15%.

## **Passive Foreign Investment Company Rules**

The Company believes that its ordinary shares and ADSs should not be treated as the stock of a passive foreign investment company, PFIC, for United States federal income tax purposes. However, this conclusion is a factual determination made annually and thus may be subject to change.

In general, we will be a PFIC with respect to a U.S. Holder if, for any taxable year in which the U.S. Holder holds the Company's ordinary shares or ADSs:

- (1) 75% or more of the gross income of the Company for the taxable year is passive income; or
- (2) 50% or more of the value (determined on the basis of quarterly averages) of the Company's assets is attributable to assets that produce or are held for the production of passive income.

Passive income generally includes dividends, interest, royalties, rents (other than certain rents and royalties derived in the active conduct of a trade or business) annuities and gains from assets that produce passive income of this nature. If a foreign corporation owns at least 25% by value of the stock of another corporation, the foreign corporation is treated for purposes of the PFIC tests as owning its proportionate share of the assets of the other corporation, and as receiving directly its proportionate share of the other corporation's income.

If the Company is treated as a PFIC, a U.S. Holder that did not make a qualified electing fund ("QEF") or mark-to-market election, each as described below, will be subject to special rules with respect to (a) any gain realized on the sale or other disposition of ordinary shares or ADSs and (b) any excess distribution by the Company to the U.S. Holder (generally, any distributions to the U.S. Holder in respect of the ordinary shares or ADSs during a single taxable year that are



greater than 125% of the average annual distributions received by the U.S. Holder in respect of the ordinary shares or ADSs during the three preceding taxable years or, if shorter, the U.S. Holder's holding period for the ordinary shares or ADSs). Under these rules:

- (1) the gain or excess distribution would be allocated ratably over the U.S. Holder's holding period for the ordinary shares or ADSs;
- (2) the amount allocated to the taxable year in which the gain or excess distribution was realized would be taxable as ordinary income;
- (3) the amount allocated to each prior year, with certain exceptions, would be subject to tax at the highest tax rate in effect for that year; and
- (4) the interest charge generally applicable to underpayments of tax would be imposed in respect of the tax attributable to each such year.

A U.S. Holder that makes a QEF election will be currently taxable on its pro rata share of the Company's ordinary earnings and net capital gain (at ordinary income and capital gain rates, respectively) for each taxable year of the Company, regardless of whether or not distributions were actually received. The U.S. Holder's basis in the ordinary shares or ADSs will be increased to reflect taxed but undistributed income. Distributions of income that had previously been taxed will result in a corresponding reduction of basis in the ordinary shares or ADSs and will not be taxed again as a distribution to the U.S. Holder.

Special rules apply with respect to the calculation of the amount of the foreign tax credit with respect to excess distributions by a PFIC or, in certain cases, QEF inclusions.

A U.S. Holder will not be subject to the PFIC tax rules described above if the U.S. Holder makes a mark-to-market election with respect to its ordinary shares or ADSs. Instead, in general, an electing U.S. Holder will include in each year, as ordinary income, the excess, if any, of the fair market value of the ordinary shares or ADSs at the end of the taxable year over their adjusted basis. These amounts of ordinary income will not be eligible for the favorable tax rates applicable to qualified dividend income or long term capital gains and will be permitted an ordinary loss in respect of the excess, if any, of the adjusted basis of the ordinary shares or ADSs over their fair market value at the end of the taxable year (but only to the extent of the net amount of previously included income as a result of the mark-to-market election). The electing U.S. Holder's basis in the ordinary shares or ADSs will be adjusted to reflect any such income or loss amounts.

In addition, notwithstanding any election by a U.S. Holder with regard to the ordinary shares or ADSs, dividends received by the U.S. Holder from the Company will not constitute qualified dividend income to the U.S. Holder, if the Company is a PFIC either in the taxable year of the distribution or the preceding taxable year. Dividends received that do not constitute qualified dividend income are not eligible for taxation at the 15% maximum rate applicable to qualified dividend income. Instead, the gross amount of any such dividend paid by the Company out of its accumulated earnings and profits (as determined for United States federal income tax purposes) is includible in the U.S. Holder's gross income and will be subject to tax at rates applicable to ordinary income.

A U.S. Holder who owns ordinary shares or ADSs during any year that the Company is a PFIC must file Internal Revenue Service Form 8621.

### **Additional United Kingdom Tax Considerations**

#### ***Gift and Inheritance Taxes***

An individual who is domiciled in the United States and who is not a national of the United Kingdom for the purposes of the Estate Tax Treaty will normally not be subject to U.K. inheritance tax in respect of the ordinary shares or ADSs on the individual's death or on a gift of the ordinary shares or ADSs during the individual's lifetime, provided that any applicable U.S. federal gift or

estate tax liability is paid, unless the ordinary shares or ADSs are part of the business property of a permanent establishment of an enterprise of the individual in the United Kingdom or pertain to a fixed base in the United Kingdom of the individual used for the performance of independent personal services.

Where the ADSs or ordinary shares have been placed in trust by a settlor who, at time of settlement, was a U.S. Holder, the ADSs or ordinary shares will normally not be subject to U.K. inheritance tax unless the settlor, at the time of settlement, was not domiciled in the United States and was a U.K. antional. In the exceptional case where the ADSs or ordinary shares are subject both to U.K. inheritance tax and to U.S. federal gift or estate tax, the Estate Tax Treaty generally provides for the tax paid in the United Kingdom to be credited against tax paid in the United States or for tax paid in the United States to be credited against tax payable in the United Kingdom based on priority rules set out in that Treaty.

#### ***Stamp Duty and Stamp Duty Reserve Tax***

A transfer for value of the ordinary shares will generally be subject to U.K. ad valorem stamp duty, normally at the rate of 0.5% of the amount or value of the consideration given for the transfer, rounded up to the nearest £5. Stamp duty is normally a payable by the Purchaser.

An agreement to transfer ordinary shares for money or money's worth will normally give rise to a charge to stamp duty reserve tax ("SDRT") at the rate of 0.5% of the amount or value of the consideration unless an instrument of transfer of the ordinary shares has been executed in pursuance of the agreement and duly stamped. SDRT is a liability of the Purchaser.

Stamp duty is charged at the higher rate of 1.5%, rounded up to the nearest £5, or SDRT at the rate of 1.5%, of the amount or value of the consideration, or in some circumstances the value of the ordinary shares, on a transfer or issue of the ordinary shares (a) to, or to a nominee for, a person whose business is or includes the provision of clearance services or (b) to, or to a nominee for, a person whose business is or includes issuing depository receipts. An election is available whereby clearance services may, under certain conditions, elect for the 0.5% rate of SDRT to apply to a transfer of shares into, and to transactions within, the service.

In accordance with the terms of the Deposit Agreement, any tax or duty payable by the Depository or the Custodian of the Depository on the deposit of ordinary shares will be charged by the Depository to the holder of the ADS.

No U.K. stamp duty will be payable on the acquisition or transfer of an ADS evidenced by an ADR or beneficial ownership of an ADR, provided that any instrument of transfer or written agreement to transfer remains at all times outside the United Kingdom. An agreement for the transfer of an ADR or beneficial ownership of an ADR will not give rise to a liability to SDRT.

Any transfer for value of the underlying ordinary shares represented by ADSs evidenced by ADRs, may give rise to a liability to U.K. stamp duty or SDRT at the rate of 0.5% as indicated above. However, on a transfer from the Custodian of the Depository to a holder of an ADS upon cancellation of the ADS a fixed U.K. stamp duty of £5 per instrument of transfer only will be payable.

#### **DOCUMENTS ON DISPLAY**

It is possible to read and copy documents referred to in this Annual Report on Form 20-F that have been filed with the SEC at the SEC's public reference room located at 450 Fifth Street, NW, Washington D.C. 20549. Please call the SEC at 1(800) SEC 0330 for further information on the public reference rooms and their copy charges. The Company's Securities and Exchange Commission filings made after November 4, 2002 are also available over the Internet at the Securities and Exchange Commission's website at <http://www.sec.gov>.

**EXEMPTIONS FROM CORPORATE GOVERNANCE LISTING REQUIREMENTS UNDER THE NASDAQ MARKETPLACE RULES**

In connection with the inclusion of our shares on the Nasdaq National Market in July 1998, the Company received an exemption from the quorum requirement under Rule 4350(f) of the Nasdaq Marketplace Rules, which requires each issuer to provide for a quorum in its by-laws for any meeting of the holders of common stock, which shall in no case be less than 33<sup>1</sup>/<sub>3</sub>% of the outstanding shares of the issuer's common voting stock. The Company's articles of association do not provide any quorum requirement for general meetings of its shareholders. This absence of a quorum requirement is in accordance with U.K. law and generally accepted business practices in the United Kingdom.

**Item 11: Quantitative and Qualitative Disclosures About Market Risk**

The Company holds financial instruments to finance its operations and to manage the currency, interest rate and liquidity risks that arise from those operations. A discussion of the Company's treasury policies employed to manage these risks is set out below. In the numerical disclosures that follow, short-term debtors and creditors that arise directly as a result of the Company's operations are excluded from all disclosures with the exception of the table below on currency exposures.

**LIQUIDITY RISK**

The Company's policy is to maintain continuity of funding through a mixture of long-term debt and bank loans, raised to cover specific projects, and through the issue of shares to collaborative partners, where necessary, to obtain development contracts. Short-term flexibility is provided through the use of overdrafts. The maturity profile of the Company's debt at December 31, 2003 is set out below.

**Maturity of financial liabilities**

	December 31, 2002	December 31, 2003	December 31, 2003 Fixed rate financial liabilities	December 31, 2003 Floating rate financial liabilities	December 31, 2003 Non-interest bearing financial liabilities
			(in £ thousands)		
Within one year	2,927	4,530	1,078	3,452	
Between one and two years	5,256	60,662	30,550	30,112	
Between two and three years	59,633	12,653	1,230	113	11,310
Between three and four years	11,573	337	223	114	
Between four and five years	381	271	157	114	
Beyond five years	5,695	9,932	3,594	2,594	3,744
	85,465	88,385	36,832	36,499	15,054

**Foreign Currency Risk**

All of the Company's operations are based overseas in Continental Europe, the United States and Canada, giving rise to exposures to changes in foreign exchange rates, notably the Swiss Franc, Euro, Swedish Krona, U.S. Dollar and Canadian Dollar. Beginning in June 1996, and where natural hedges have not been sufficient or possible, the Company has selectively entered into forward currency contracts to fix certain of the non-sterling funding requirements of its principal subsidiaries. The contracts generally have maturities not exceeding twelve months. Gains or losses

on these contracts are not recorded until the maturity of the contracts at which time they are recorded as an adjustment to administrative expenses, consistent with the underlying non-sterling expenses that are required to be funded. During 2000, £59.4 million of funding was raised in sterling, and as a result, since then, the Group has actively used forward currency contracts and currency options. No gain or loss was recognized on such contracts during 2002 or 2003.

At December 31, 2002, the Company had European style accrual forward options to purchase £154,000 of Swiss francs each week for the 26 weeks ending in July 2002 and £71,000 of Euro each week for the 14 weeks ending in April 2002. At December 31, 2002, the Company had agreements in place for American style accrual forward options, commencing in January 2003, to purchase £113,000 U.S. dollars for the 44 weeks ending in November 2003 and £44,000 of Swedish Krona each week for the 45 weeks ending in November 2003. Both of these structures lapsed in January and February 2003 respectively. At December 31, 2002, the Company had forward currency contracts to purchase £4.5 million of Swiss francs, £1.1 million of Euro and £0.5 million of Swedish Krona. The unrecognized gain from such contracts at December 31, 2002 was £48,000.

At December 31, 2003, the Company had European style accrual forward options to purchase £142,000 of Sterling each week for the 4 weeks ending in January 2004, £22,000 of Euro each week for the 8 weeks ending in February 2004 and £123,000 of Swiss Francs each week for the 36 weeks ending in September 2004. In addition, the Company has an agreement to purchase £0.5 million of Swedish Krona at agreed rates each month for the 6 months ending in June 2004. At December 31, 2003, the Company had forward currency contracts to purchase £4.6 million of Euro, £2.3 million of U.S. dollars, £0.3 million of Swedish Krona and to sell £0.3 million of Swiss Francs. The unrecognized gain from such contracts at December 31, 2003 was £32,000.

The analysis below shows the net monetary assets and liabilities of Group companies that are not denominated in their functional currency and therefore give rise to exchange gains and losses in the income statements in both 2003 and 2002.

*Currency exposures*

**December 31, 2003**

**Functional currency of Operating Company**

Net foreign currency monetary assets/(liabilities)						
Swedish Krona	Sterling	\$U.S.	Euro	Swiss francs	\$Canadian	Total
(in thousands)						
Sterling		3,796	847		6	4,649
\$U.S.	(3,579)		(65)			(3,644)
Euro	245	(17)		2,622		2,850
Swiss francs	(5)	10,280	2,419	(220)		12,474
\$Canadian		1,038	(1,391)	(71)		(424)
Swedish Krona	(2,568)	(54)				(2,622)
	(5)	5,416	4,753	491	2,622	6
						13,283

December 31, 2002

## Functional currency of Operating Company

## Net foreign currency monetary assets/(liabilities)

	Sterling	\$U.S.	Euro	Swiss francs	\$Canadian	Total
(in thousands)						
Sterling		2,232	617		1	2,850
\$U.S.	(15,956)		(9)		(34)	(15,999)
Euro	(2,025)	96		2,225		296
Swiss francs	(928)	3,142	(528)		(582)	1,104
\$Canadian	1,904	400	(130)	550		2,724
Swedish Krona	(1,343)					(1,343)
	(18,348)	5,870	(50)	2,775	(615)	(10,368)

## Interest Rate Risk

The Company borrows at fixed and floating rates of interest as deemed appropriate for its circumstances. Where necessary, the Company uses interest rate swaps to achieve the desired interest rate profile. From February 27, 2002, £30 million of the £59.4 million convertible bond liability was the subject of a new cancelable interest rate swap agreement by which the Company swapped the 6.0% fixed rate obligation to a floating rate and paid 5.6%. On December 19, 2002, this swap was cancelled and replaced by a subsequent swap agreement whereby £30.0 million of the £59.4 million convertible bond liability was the subject of a cancelable interest rate swap agreement by which the Company swapped the fixed obligation to pay 6.0% to floating 5.75%. This facility remained in place throughout most of 2003. The weighted average floating rate for 2003 was 5.77%, and the floating rate at December 31, 2003 was 6.35%. The Company's management have assessed remaining interest rate exposures and deemed them not to be material. The interest rate and currency profile of the Company's financial assets and liabilities is set out below.

## Interest rate and currency profile of financial assets

December 31, 2003

## Currency

	Fixed rate financial assets	Weighted average interest rate on fixed financial assets	Weighted average time for which rate is fixed	Floating rate financial assets	Non-interest bearing financial assets	Total financial assets
	£'000	%	(months)	£'000	£'000	£'000
Sterling	7,981	4.94	15.2	6,016	2,129	16,126
\$U.S.	568	12.00	59.5	7,335	18,728	26,631
Swiss francs				192	2	194
\$Canadian				821	629	1,450
Euro				1,170	64	1,234
Swedish Krona				610		610
	8,549	5.41	18.1	16,144	21,552	46,245

Edgar Filing: SKYEPHARMA PLC - Form 20-F

December 31, 2002

Currency

	Fixed rate financial assets	Weighted average interest rate on fixed financial assets	Weighted average time for which rate is fixed	Floating rate financial assets	Non-interest bearing financial assets	Total financial assets
	£'000	%	(months)	£'000	£'000	£'000
Sterling	1,961	5.00	54.0	18,680	36	20,677
\$U.S.				4,292	16,663	20,955
Swiss francs				1,870		1,870
\$Canadian				2,026	2,228	4,254
Euro				617		617
Swedish Krona				523		523
	<b>1,961</b>	<b>5.00</b>	<b>54.0</b>	<b>28,008</b>	<b>18,927</b>	<b>48,896</b>

Total financial assets comprise fixed asset investments of £22.0 million (2002: £18.9 million), current asset investments of £1.0 million (2002: £2.0 million) and cash and short-term bank deposits of £23.2 million (2002: £28.1 million).

Floating rate financial assets bear interest at rates based upon the floating bank rate in the country in which the funds are held. Non-interest bearing financial assets consist of balances held in short-term current accounts.

*Interest rate and currency profile of financial liabilities*

December 31, 2003

Currency

	Fixed rate financial liabilities	Weighted average interest rate on fixed financial liabilities	Weighted average time for which rate is fixed	Floating rate financial liabilities	Non-interest bearing financial liabilities	Weighted average time to maturity (months)	Total financial liabilities
	£'000	%	(months)	£'000	£'000	(months)	£'000
Sterling	29,400	6.00	17.5	30,000	11,310	28.0	70,710
\$U.S.	2,701	7.99	35.7	559	3,070	136.0	6,330
Swiss francs	4,496	3.66	23.0	5,940			10,436
\$Canadian					389	120.0	389
Euro					285	405.0	285
Swedish Krona	235	6.38	26.2				235
	<b>36,832</b>	<b>5.86</b>	<b>19.6</b>	<b>36,499</b>	<b>15,054</b>	<b>59.6</b>	<b>88,385</b>

December 31, 2002

## Currency

	Fixed rate financial liabilities	Weighted average interest rate on fixed financial liabilities	Weighted average time for which rate is fixed	Floating rate financial liabilities	Non-interest bearing financial liabilities	Weighted average time to maturity	Total financial liabilities
	£'000	%	(months)	£'000	£'000	(months)	£'000
Sterling	29,400	6.00	29.5	30,000	11,310	40.0	70,710
Swiss francs	4,560	3.64	13.5	4,897			9,457
Euro	863	6.25	11.0		201	417.0	1,064
\$US	25	5.25	40.0	621	3,269	144.0	3,915
Swedish Krona	319	7.25	27.8				319
	35,167	5.71	27.0	35,518	14,780	68.1	85,465

Financial liabilities comprise total borrowings of £13.6 million (2002: £10.0 million), convertible bonds of £59.4 million (2002: £59.4 million), non-equity Deferred "B" Shares of £11.3 million (2002: £11.3 million), other creditors of £3.8 million (2002: £4.6 million) and provisions of £0.3 million (2002: £0.2 million).

The effect of the Group's interest rate swap is to classify £30.0 million of the convertible bond in the above table as a floating rate financial liability. Total financial liabilities does not agree to the total of the balance sheet captions due to the presence of £609,000 (2002: £1,023,000) of unamortized issue costs within the value shown on the balance sheet for convertible bonds. Certain financial instruments, such as currency options, are excluded from the analysis above where they do not alter the interest basis or currency of financial liabilities.

All other floating rate financial liabilities, in both 2003 and 2002, are interest bearing financial liabilities that bear interest at interest rates based on LIBOR, prime and other bank based lending rates in the country in which the liability arises, which are fixed for periods of up to 12 months.

## Credit Risk

The Company is exposed to credit-related losses in the event of non-performance by third parties to financial instruments. The Company does not expect any third parties to fail to meet their obligations given the policy of selecting only parties with high credit ratings and minimizing its exposure to any one institution.

## Fair Values

The comparison of fair and book values of all the Company's financial instruments as at December 31, 2003 is set out below. Market values have been used to determine the fair values of all swaps and foreign currency contracts. The fair value of the non-equity Deferred "B" Shares has been calculated by reference to the ordinary share price at December 31, 2003, based upon the Director's opinion that 12 million ordinary shares will be issued in settlement of the deferred consideration payable on the acquisition of Jago. See "Item 7: Major Shareholders and Related Party Transactions - Certain Arrangements in Respect of the Jago Acquisition" for details of the contingencies governing the issuance of these shares. The fair values of all other items have been calculated by discounting future cash flows at interest rates prevailing at December 31, 2003.

Edgar Filing: SKYEPHARMA PLC - Form 20-F

December 31, 2003

	<u>Book Values</u>	<u>Fair values</u>
	(in £ thousands)	
<b>Financial instruments held or issued to finance the Group's operations</b>		
Fixed asset investments	22,024	28,745
Current asset investments	981	981
Cash at bank and in hand	3,052	3,052
Short-term bank deposits	20,188	20,188
Short-term borrowings and current portion of long-term borrowings	(4,530)	(4,530)
Long-term convertible debt	(59,400)	(56,218)
Other long-term debt	(13,145)	(13,145)
Non-equity Deferred 'B' Shares	(11,310)	(9,030)
	<u>(42,140)</u>	<u>(29,957)</u>
<b>Derivative financial instruments held to manage the Group's currency profile</b>		
Interest rate swaps		322
Canadian \$ currency options		
Euro currency options		(21)
Swiss franc currency options		12
Swedish Krona currency options		59
Forward currency contracts		(18)
		<u>354</u>

December 31, 2002

	<u>Book Values</u>	<u>Fair values</u>
	(in £ thousands)	
<b>Financial instruments held or issued to finance the Group's operations</b>		
Fixed asset investments	18,874	17,287
Current asset investments	1,961	1,961
Cash at bank and in hand	7,394	7,394
Short-term bank deposits	20,667	20,667
Short-term borrowings and current portion of long-term borrowings	(2,927)	(2,927)
Long-term convertible debt	(59,400)	(53,863)
Other long-term debt	(11,828)	(11,707)
Non-equity Deferred 'B' Shares	(11,310)	(4,980)
	<u>(36,569)</u>	<u>(26,168)</u>
<b>Derivative financial instruments held to manage the Group's currency profile</b>		
Interest rate swaps		452
Euro currency options		(85)
U.S.\$ currency options		(13)
Forward currency contracts		146
		<u>500</u>

The excess of fair values over book values for currency options and forward currency contracts shown in the table above represents the unrecognized hedging gain on these instruments as at





Edgar Filing: SKYEPHARMA PLC - Form 20-F

December 31, 2003. The actual gains or losses arising on these options will be dependent on future exchange rates and will be recognized in the profit and loss account, in 2003, as the operational transactions to which they are linked occur. The table below shows the extent to which the Company has off-balance sheet (unrecognized) and on-balance sheet (deferred) gains and losses in respect of hedges at the beginning and end of the year ended December 31, 2003.

**December 31, 2003**

	Unrecognized			Deferred		
	Gains	Losses	Net Total	Gains	Losses	Net Total
	(in £ thousands)					
Gains/(losses) on hedges at January 1, 2003	598	(98)	500			
Changes in value from January 1, 2003 to settlement	6	85	91			
<b>Gains/(losses) arising in previous years recognized in 2003</b>	(152)	13	(139)			
Gains/(losses) not recognized in 2003 arising before January 1, 2003	452		452			
Arising in 2003	(59)	(39)	(98)			
<b>Gains/(losses) on hedges at December 31, 2003</b>	<b>393</b>	<b>(39)</b>	<b>354</b>			

**December 31, 2002**

	Unrecognized			Deferred		
	Gains	Losses	Net Total	Gains	Losses	Net Total
	(in £ thousands)					
Gains/(losses) on hedges at January 1, 2002		(31)	(31)		(20)	(20)
Changes in value from January 1, 2002 to settlement		262	262			
<b>Gains/(losses) arising in 2001 recognized in 2002</b>		231	231		(20)	(20)
Gains/(losses) not recognized in 2002 arising before January 1, 2002						
Arising in 2002	598	(98)	500			
<b>Gains/(losses) on hedges at December 31, 2002</b>	<b>598</b>	<b>(98)</b>	<b>500</b>			

Unrecognized gains at December 31, 2003 include £0.3 million in relation to the cancelable interest rate swap agreement. This was based upon the agreement continuing for the life of the convertible bonds and as such the gain would have been spread in the profit and loss account until 2005.

**Item 12: Description of Securities other than Equity Securities**

Not applicable

**PART II**

**Item 13: Defaults, Dividend Arrearages and Delinquencies**

None

**Item 14: Material Modifications to the Rights of Security Holders and Use of Proceeds**

None

**Item 15: Controls and Procedures**

As of December 31, 2003 (the "Evaluation Date"), an evaluation was performed under the supervision and with the participation of the Company's management, including the Chief Executive Officer and the Chief Financial Officer, of the effectiveness of the design and operation of the Company's disclosure controls and procedures (as defined in Exchange Act Rules 13a-14(c) and 15d-14(c)). Based on that evaluation, the Company's management, including the Chief Executive Officer and the Chief Financial Officer, concluded that the Company's disclosure controls and procedures were effective at the level of providing reasonable assurance as of the Evaluation Date. There have been no significant changes in 2003 in the Company's internal control over financial reporting, including any corrective actions with regard to significant deficiencies and material weaknesses, or in other factors that have materially affected, or are reasonably likely to materially affect, the Company's internal control over financial reporting. In designing and evaluating the Company's disclosure controls and procedures, the Company's management, including the Chief Executive Officer and the Chief Financial Officer, recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and the Company's management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been detected.

**Item 16A: Audit Committee Financial Expert**

The Company does not have an Audit Committee financial expert serving on its Audit Committee. The Company's Board of Directors has determined that, whilst no one member of the Audit Committee possesses all of the attributes of the definition of a financial expert, the Audit Committee members collectively possess such attributes. As such, the Board believes that the committee has the appropriate collective requirements.

**Item 16B: Code of Ethics**

On April 28, 2004 the Company adopted a Code of Business Conduct and Ethics which is applicable to all directors, officers and employees. A copy of the Code is posted on the Company's internet website at [www.skyepharma.com](http://www.skyepharma.com).

**Item 16C: Principal Accountant Fees and Services**

During 2002 and 2003 the Company (including its overseas subsidiaries) obtained the following services from its auditor for the fees set forth below:

	Year to December 31,	
	2002	2003
	(in £ thousands)	
Audit fees	354	326
Audit related fees	160	145
Tax fees	681	751
All other fees	418	252
	1,613	1,474

Audit related fees include fees paid for assurance and related services such as the review of the Company's interim report. Tax fees include fees paid for compliance, advisory and planning services. All other fees include fees paid for due diligence, accounting advice and assistance in connection with the preparation of regulatory returns.

The Audit Committee has in place pre-approval policies and procedures, which were adopted on March 26, 2003. The pre-approved engagements are specified in reasonable detail in the pre-approval policies and procedures and generally include all services requiring an independent, objective assessment of information or procedures and advice on areas core to the financial statements and audit. In particular, pre-approved engagements include services relating to external reporting, acquisitions, disposals, taxation and general accounting.

All engagements not covered by the pre-approval policies and procedures are subject to pre-approval on a case-by-case basis.

The Audit Committee is informed of each engagement entered into pursuant to the pre-approved policies and procedures at its next scheduled meeting.

All services for which PricewaterhouseCoopers LLP was engaged subsequent to May 6, 2003 have been pre-approved.

**Item 16D: Exemption from the Listing Standards for Audit Committee**

Not applicable

**Item 16E: Purchases of Equity Securities by the Issuer and Affiliated Purchasers**

Not yet applicable

**PART III**

**Item 17: Financial Statements**

The Company is furnishing financial statements pursuant to the instructions of Item 18 of Form 20-F. See "Item 18: Financial Statements".

**Item 18: Financial Statements**

The following financial statements, together with the report thereon, by PricewaterhouseCoopers LLP, are filed as part of this Form 20-F:

Report of Independent Registered Public Accounting Firm	F-1
SkyePharma PLC Consolidated Financial Statements	
Consolidated Income Statements for the years ended December 31, 2001, 2002 and 2003	F-2
Consolidated Balance Sheets at December 31, 2002 and 2003	F-3
Consolidated Cash Flow Statements for the years ended December 31, 2001, 2002 and 2003	F-4
Notes to the Consolidated Cash Flow Statements	F-5
Statement of Total Recognized Gains and Losses	F-8
Reconciliation of Movement in Shareholders' Funds	F-9
Notes to the Consolidated Financial Statements	F-10

**SIGNATURES**

The registrant hereby certifies that it meets all of the requirements for filing on Form 20-F and that it has duly caused and authorized the undersigned to sign this Annual Report on its behalf.

Date: June 28, 2004

SKYEPHARMA PLC  
(Registrant)

By: /s/ Donald Nicholson

\_\_\_\_\_  
Name: Donald Nicholson

Title: Finance Director

---

**REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

**To the Board of Directors and Shareholders of SkyePharma PLC**

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of income, of cash flows, of total recognized gains and losses and of movements in shareholders' funds present fairly, in all material respects, the financial position of SkyePharma PLC and its subsidiaries at December 31, 2003 and 2002 and the results of their operations and their cash flows for the three years in the period ended December 31, 2003 in conformity with accounting principles generally accepted in the United Kingdom. These financial statements are the responsibility of the Company's management; our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). These standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

Accounting principles generally accepted in the United Kingdom vary in certain significant respects from accounting principles generally accepted in the United States of America. Information relating to the nature and effect of such differences is presented in Note 32 to the Consolidated Financial Statements.

**PricewaterhouseCoopers LLP**

London  
United Kingdom

May 5, 2004

F-1

---



## SKYEPHARMA PLC

## Consolidated Income Statements

	Notes	Before amortization £'000	Amortization £'000	Year to December 31, 2001 £'000	Before amortization £'000	Amortization £'000	Year to December 31, 2002 £'000	Before exceptional items and amortization £'000	Exceptional items and amortization (note 4) £'000	Year December 2002 £'000
<b>Turnover</b>	2	46,126		46,126	69,573		69,573	53,152		53,152
Cost of sales	2	(18,820)		(18,820)	(24,830)		(24,830)	(29,786)		(29,786)
<b>Gross profit</b>		27,306		27,306	44,743		44,743	23,366		23,366
Selling, marketing and distribution expenses		(4,804)		(4,804)	(4,769)		(4,769)	(4,348)		(4,348)
Administration expenses			(3,824)	(3,824)		(6,506)	(6,506)		(6,669)	(6,669)
Amortization Other administration expenses including exceptional impairments		(12,201)		(12,201)	(13,686)		(13,686)	(17,987)	(9,487)	(23,474)
		(12,201)	(3,824)	(16,025)	(13,686)	(6,506)	(20,192)	(17,987)	(16,156)	(36,148)
Research and development expenses		(17,918)		(17,918)	(29,285)		(29,285)	(30,520)		(30,520)
Other operating income	3	6,342		6,342	14,219		14,219	6,126		6,126
<b>Operating (loss)/profit</b>	5	(1,275)	(3,824)	(5,099)	11,222	(6,506)	4,716	(23,363)	(16,156)	(16,156)
Associated undertaking Share of loss of associated undertaking		(75)		(75)						
Amortization			(503)	(503)						
		(75)	(503)	(578)						
<b>Total operating (loss)/profit: Group and share of associates</b>		(1,350)	(4,327)	(5,677)	11,222	(6,506)	4,716	(23,363)	(16,156)	(16,156)
Interest receivable	7	1,251		1,251	1,081		1,081	1,029		1,029
Interest payable	8	(4,951)		(4,951)	(4,464)		(4,464)	(4,493)		(4,493)
<b>(Loss)/profit on ordinary activities before taxation</b>	2	(5,050)	(4,327)	(9,377)	7,839	(6,506)	1,333	(26,827)	(16,156)	(16,156)
Taxation	9	(75)		(75)	(224)		(224)	(240)		(240)
<b>Retained (loss)/profit</b>		(5,125)	(4,327)	(9,452)	7,615	(6,506)	1,109	(27,067)	(16,156)	(16,156)
<b>Earnings per Ordinary Share</b>	10									
Basic		(1.0p)	(0.8p)	(1.8p)	1.3p	(1.1p)	0.2p	(4.4p)	(2.7p)	(2.7p)
Diluted		(1.0p)	(0.8p)	(1.8p)	1.3p	(1.1p)	0.2p	(4.4p)	(2.7p)	(2.7p)

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Notes	Before amortization £'000	Amortization £'000	Year to December 31, 2001 £'000	Before amortization £'000	Amortization £'000	Year to December 31, 2002 £'000	Before exceptional items and amortization £'000	Exceptional items and amortization (note 4) £'000	Year December 200 £'00

There was no material difference between the (loss)/profit on ordinary activities before taxation and historic cost (loss)/profit before taxation for these periods. All results represent continuing activities.

See Notes to the Financial Statements.

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Consolidated Balance Sheets

	Notes	December 31, 2002 £'000	December 31, 2003 £'000
<b>Fixed assets</b>			
Intangible assets	11	100,015	95,096
Tangible assets	12	45,504	42,615
Investments	13	19,902	23,419
		165,421	161,130
<b>Current assets</b>			
Stock	14	1,256	1,320
Debtors	15	35,207	15,634
Investments	16	1,961	981
Cash and short-term bank deposits		28,061	23,240
		66,485	41,175
<b>Creditors: amounts falling due within one year</b>			
Deferred income		(15,069)	(12,926)
Other creditors		(19,402)	(26,394)
	17	(34,471)	(39,320)
<b>Net current assets</b>		32,014	1,855
<b>Total assets less current liabilities</b>		197,435	162,985
<b>Creditors: amounts falling due after more than one year</b>			
Convertible bonds due June 2005		(58,377)	(58,791)
Deferred income		(2,960)	(2,948)
Other creditors		(11,627)	(12,860)
	18	(72,964)	(74,599)
<b>Provisions for liabilities and charges</b>	19	(201)	(2,121)
<b>Net assets</b>		124,270	86,265
<b>Capital and reserves</b>			
Share capital	23	62,546	63,067
Share premium	25	316,419	319,223
Other reserves	25	9,311	9,350
Profit and loss account	25	(264,006)	(305,375)
<b>Shareholders' funds</b>		112,960	74,955
Attributable to equity interests		112,960	74,955
Attributable to non-equity interests		11,310	11,310
		124,270	86,265

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

For details of contingent liabilities and commitments, see Notes 21 and 22 to the Financial Statements.  
See Notes to the Financial Statements.

F-3

---

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Consolidated Cash Flow Statements

	Notes	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>Net cash inflow from operating activities</b>	(b)	5,909	1,552	6,615
<b>Returns on investments and servicing of finance</b>				
Interest received		2,741	943	1,047
Interest paid		(4,370)	(3,913)	(4,013)
Interest element of finance lease payments		(170)	(130)	(70)
		<u>(1,799)</u>	<u>(3,100)</u>	<u>(3,036)</u>
<b>Taxation</b>		<u>(75)</u>	<u>(224)</u>	<u>(227)</u>
<b>Capital expenditure and financial investment</b>				
Purchase of intangible fixed assets		(310)	(3,035)	(2,530)
Purchase of tangible fixed assets		(7,673)	(3,238)	(4,021)
Purchase of fixed asset investments		(8,273)	(6,285)	(5,674)
		<u>(16,256)</u>	<u>(12,558)</u>	<u>(12,225)</u>
<b>Acquisitions</b>	(d)			
Purchase of drug delivery business of Bioglan AB			(3,595)	
Purchase of RTP Pharma Inc.		(4,118)		
Net cash acquired with RTP Pharma Inc.		5,436		
		<u>1,318</u>	<u>(3,595)</u>	
<b>Cash outflow before use of liquid resources and financing</b>		<u>(10,903)</u>	<u>(17,925)</u>	<u>(8,873)</u>
<b>Management of liquid resources</b>				
Net decrease/(increase) in amounts held on short-term bank deposit		14,668	(3,872)	183
<b>Financing</b>				
Issue of Ordinary Share capital		468	26,168	1,437
Issue of warrants			311	39
Debt due within one year:				
Inception of new loan				770
Repayment of loans		(4,502)	(2,992)	
Debt due beyond one year:				
Inception of new loan				1,936
Repayment of loans		(85)	(929)	(286)
Capital element of finance lease payments		(772)	(937)	(1,078)
		<u>(4,891)</u>	<u>21,621</u>	<u>2,818</u>
<b>Decrease in cash</b>		<u>(1,126)</u>	<u>(176)</u>	<u>(5,872)</u>

See Notes to the Consolidated Cash Flow Statement.



## Notes to the Consolidated Cash Flow Statements

## (a) Reconciliation of movements in net debt

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Decrease in cash in the year	(1,126)	(176)	(5,872)
Cash outflow/(inflow) from decrease/(increase) in debt and lease financing	5,454	4,858	(1,342)
Cash (inflow)/outflow from (decrease)/increase in liquid resources	(14,668)	3,872	(183)
Change in net debt resulting from cash flows	(10,340)	8,554	(7,397)
Finance leases acquired with subsidiary		(361)	
New finance leases	(95)	(91)	(46)
Amortization of issue costs on convertible bond	(416)	(415)	(414)
Chiron promissory note		(621)	
Translation difference	(21)	(1,505)	(24)
Movement in net debt in the year	(10,872)	5,561	(7,881)
Net debt at beginning of the year	(36,290)	(47,162)	(41,601)
Net debt at end of the year	(47,162)	(41,601)	(49,482)

Net debt is defined as cash and liquid resources less borrowings.

## (b) Reconciliation of operating (loss)/profit to net cash inflow from operating activities

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Operating (loss)/profit	(5,099)	4,716	(39,519)
Depreciation	4,778	6,101	6,294
Amortization	3,824	6,506	6,669
(Increase)/decrease in stock and work in progress	(642)	1,022	(64)
(Increase)/decrease in debtors	(7,478)	(21,585)	19,573
Increase/(decrease) in deferred income excluding unrealized gain on contract development	11,690	6,339	(126)
Increase/(decrease) in other creditors	1,688	(313)	4,734
(Decrease)/increase in provisions	(2,051)	133	1,920
Impairment of intellectual property			2,673
Impairment of tangible fixed assets			1,324
Write down of fixed asset investments			1,599
Other	(801)	(1,367)	1,538
Net cash inflow from operating activities	5,909	1,552	6,615

## c) Analysis of net debt

	At January 1, 2001 £'000	Cash flow £'000	Acquisitions (excl cash & overdrafts) £'000	Non-cash changes £'000	Exchange movement £'000	At December 31, 2001 £'000
Cash at bank and in hand	10,769	(1,502)			184	9,451
Bank overdraft	(2,848)	376		828	26	(1,618)
Short-term bank deposits	32,109	(14,668)				17,441
	40,030	(15,794)		828	210	25,274
Debt due within one year	(6,231)	4,502		(2,936)	(127)	(4,792)
Debt due after one year	(9,995)	85		2,108	(159)	(7,961)
Convertible bonds	(57,546)			(416)		(57,962)
Finance leases	(2,548)	772			55	(1,721)
	(76,320)	5,359		(1,244)	(231)	(72,436)
	(36,290)	(10,435)		(416)	(21)	(47,162)
	At January 1, 2002 £'000	Cash flow £'000	Acquisitions (excl cash & overdrafts) £'000	Non-cash changes £'000	Exchange movement £'000	At December 31, 2002 £'000
Cash at bank and in hand	9,451	(1,828)			(229)	7,394
Bank overdraft	(1,618)	1,652			(34)	
Short-term bank deposits	17,441	3,872			(646)	20,667
	25,274	3,696			(909)	28,061
Debt due within one year	(4,792)	2,992			(42)	(1,842)
Debt due after one year	(7,961)	929		(621)	(470)	(8,123)
Convertible bonds	(57,962)			(415)		(58,377)
Finance leases	(1,721)	937	(361)	(91)	(84)	(1,320)
	(72,436)	4,858	(361)	(1,127)	(596)	(69,662)
	(47,162)	8,554	(361)	(1,127)	(1,505)	(41,601)



Edgar Filing: SKYEPHARMA PLC - Form 20-F

	At January 1, 2003 £'000	Cash flow £'000	Acquisitions (excl cash & overdrafts) £'000	Non-cash changes £'000	Exchange movement £'000	At December 31, 2003 £'000
Cash at bank and in hand	7,394	(4,666)			324	3,052
Bank overdraft		(1,206)			8	(1,198)
Short-term bank deposits	20,667	(183)			(296)	20,188
	28,061	(6,055)			36	22,042
Debt due within one year	(1,842)	(770)		(559)	(1)	(3,172)
Debt due after one year	(8,123)	(1,650)		559	19	(9,195)
Convertible bonds	(58,377)			(414)		(58,791)
Finance leases	(1,320)	1,078		(46)	(78)	(366)
	(69,662)	(1,342)		(460)	(60)	(71,524)
	(41,601)	(7,397)		(460)	(24)	(49,482)

Cash at bank and in hand and short-term bank deposits are aggregated on the balance sheet. Debt includes bank loans, a secured mortgage, the Chiron promissory note and convertible bonds. See note 17; Creditors: Amounts Falling Due Within One Year and note 18; Creditors: Amounts Falling Due After More Than One Year.

Non-cash changes in 2003 relate to the amortization of the issue costs on the convertible bonds, the inception of new finance leases and transfers between categories.

**(d) Purchase of subsidiary undertakings and businesses**

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Net assets/(liabilities) acquired	5,935	(375)	
Goodwill	29,901	3,970	
Net consideration	35,836	3,595	
Satisfied by:			
Shares issued/allocated	29,536		
Shares to be issued/allocated	5,780		
Cash	3,528	3,500	
Expenses relating to the transaction	590	95	
Demand notes	(3,598)		
	35,836	3,595	
Cash consideration	(3,528)	(3,500)	
Expenses relating to transaction	(590)	(95)	
Net cash acquired with subsidiary	5,436		
Net cash inflow/(outflow) on purchase of subsidiaries and businesses	1,318	(3,595)	

See Note 29; Acquisitions

F-7

---

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Statement of Total Recognized Gains and Losses

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>(Loss)/profit attributable to shareholders</b>	(9,452)	1,109	(43,223)
Net currency translation effect	28	903	(175)
Lapse of warrants	271	1,096	
Unrealized gain on contract development			2,029
<b>Total recognized gains and losses for the year</b>	(9,153)	3,108	(41,369)

F-8

## Reconciliation of Movement in Shareholders' Funds

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Shareholders' funds at the beginning of the year	68,952	95,145	124,270
Total recognized gains and losses for the year	(9,153)	3,108	(41,369)
Equity shares issued, net of expenses	29,599	43,816	2,560
Exercise of share options, net of expenses	459	700	765
Issue of warrants		311	39
Goodwill adjustments on deferred consideration	148	4,837	
Non equity shares converted to equity shares		(11,310)	
Increase/(decrease) in shares and warrants to be issued	5,780	(5,780)	
Revaluation of shares and warrants to be issued	(148)	(4,837)	
Exercise of warrants	(56)	(624)	
Lapse of warrants	(436)	(1,096)	
Net movement in the year	26,193	29,125	(38,005)
Shareholders' funds at the end of the year	95,145	124,270	86,265

F-9

## **1 Accounting Policies**

### **Accounting convention and presentation**

The financial statements have been prepared under the historical cost convention and in accordance with the Companies Act 1985 and applicable U.K. accounting standards. The principal accounting policies have been applied consistently and are set out below. The results for the year all relate to continuing operations. The financial statements have been prepared on a going concern basis.

### **Consolidation**

The consolidated financial information includes the financial statements for the Company, its subsidiary undertakings and the Group's share of the net assets and results of associated undertakings. Intra-Group sales and profits are eliminated fully on consolidation. The results of subsidiaries sold or acquired are included in the consolidated profit and loss account up to the date of their sale or from their date of acquisition respectively. The share of results of associated undertakings sold or acquired are included in the profit and loss account up to the date of their sale or from the date of their acquisition respectively.

### **Revenue recognition**

Turnover comprises contract development and licensing, royalty and manufacturing and distribution income. Contract development and licensing income represents amounts invoiced to customers for services rendered under development and licensing agreements, including milestone payments and technology access fees. Contract revenue is recognized when earned and non-refundable and to the extent that there are no future obligations pursuant to the revenue, in accordance with the contract terms. Refundable contract revenue is treated as deferred until such time as it is no longer refundable. Royalty income represents income earned as a percentage of product sales. Advance royalties received are treated as deferred income until earned, when they are recognized as income. Manufacturing and distribution revenues principally comprise contract manufacturing fees invoiced to third parties and income from product sales.

### **Research and development costs**

Research and development costs are charged as an expense in the period in which they are incurred.

### **Foreign currency transactions**

Foreign currency transactions by Group companies are recorded in local currency at the exchange rate ruling on the date of transaction. Assets and liabilities expressed in foreign currencies are translated into sterling at the exchange rates ruling at the balance sheet date. Exchange differences which relate to the retranslation of net assets of overseas companies are taken directly to reserves. All other foreign exchange differences are taken to the profit and loss account in the year in which they arise. The Group uses the average exchange rates prevailing during the year to translate the results of overseas subsidiaries into sterling and year-end rates to translate the net assets of those undertakings.

### **Pension costs**

The costs of the Group's defined contribution pension arrangements are charged to the profit and loss account in the year to which they relate. The costs of the Group's defined benefits scheme are charged on a systematic basis allowing for the expected pension cost over the service lives of employees, based on actuarial advice.

### Employee Share Plans

Incentives in the form of shares are provided to employees under share option and share award schemes. In respect of award schemes the Group provides finance to an employee share ownership trust to purchase company shares on the open market to meet the Group's obligation to provide shares when employees exercise their award. The difference between the purchase price of the shares and the exercise price of the award is charged, or credited, to the profit and loss account over the periods of service in respect of which the award was granted.

The costs of running the employee share ownership trust are charged to the profit and loss account as they accrue.

Shares held by the employee share ownership trust are accounted for as fixed asset investments at cost less accrual for costs charged.

### Intangible fixed assets

Intangible fixed assets comprise goodwill, intellectual property and capitalized development costs. Goodwill, being the difference between the fair value of the purchase consideration and the Group's share of the fair value of the net assets acquired, is capitalized and amortized over a period of 20 years or less in line with the Directors' view of its useful economic life. Prior to the introduction of FRS 10; Goodwill and intangible assets, the policy adopted was to write off goodwill to reserves. As permitted by FRS 10 goodwill written off to reserves in previous years has not been reinstated on the balance sheet and adjustments to such goodwill have been taken directly to reserves. Goodwill previously written off to reserves is charged to the profit and loss account in the event of disposal of the related business.

Intellectual property comprises acquired patents, trademarks, know-how and other similarly identified rights. These are recorded at their fair value at acquisition date and are amortized in equal instalments over their estimated useful economic lives, from the date when the transfer of technology is complete. The period over which the Group expects to derive economic benefits does not exceed 20 years. Costs associated with internally developed intellectual property are generally treated as research and development costs.

### Tangible fixed assets

Tangible fixed assets are included in the balance sheet at cost less accumulated depreciation. Depreciation is provided on tangible fixed assets at rates calculated to write off the cost, less estimated residual value, of each asset over its expected useful life. The rates and bases are as follows:

Freehold land	not depreciated
Freehold buildings	2% 5% straight line
Short leasehold property	period of lease
Plant, equipment and fixtures	10% 33% straight line
Motor vehicles	20% straight line
Finance leases	period of lease

### Fixed asset investments

Investments that are held for continuing use in the business are classified as fixed asset investments and recorded in the balance sheet at cost or Directors' valuation, less provision for permanent diminution in value.

### **Impairment of fixed assets**

The carrying values of fixed assets are reviewed for impairment when there is an indication that the assets may be impaired. First year impairment reviews are conducted for acquired goodwill and intangible assets. Impairment is determined by reference to the higher of net realisable value and value in use, which is measured by reference to discounted future cash flows. Any provision for impairment is charged to the profit and loss account in the year concerned.

### **Stock and work-in-progress**

Stock and work-in-progress are valued at the lower of cost and net realisable value and calculated using the first-in, first-out basis.

### **Current asset investments**

Investments held other than for continuing use in the business are classified as current asset investments and recorded in the balance sheet at the lower of cost and net realizable value.

### **Liquid resources**

Liquid resources comprise short-term bank and commercial deposits with a maturity of less than one year.

### **Leased and hired assets**

Leasing agreements which transfer to the Group substantially all of the risks and rewards of ownership of an asset are treated as finance leases. The assets are included in tangible fixed assets and the capital element of amounts owed to the finance company at the balance sheet date is included in creditors as amounts falling due either within or after more than one year. Repayments are treated as consisting of both capital and interest with the interest element being charged to the profit and loss account in proportion to the outstanding obligations. Payments under operating leases and short-term hire contracts are charged to the profit and loss account as they fall due.

### **Convertible debt**

On issue, convertible debt is stated at the amount of net proceeds after deducting issue costs. On conversion the amount recognised in shareholders' funds in respect of the shares issued is equal to the carrying value at the date of conversion. Interest payable on convertible debt is calculated to unwind the issue costs and any discount on issue at a constant rate over the term of the debt.

### **Deferred consideration**

Provisions for deferred consideration comprise the fair value of contingent consideration arising from acquisitions. The eventual outcome is subject to the Group's future performance and certain contractual terms. Provisions are reviewed annually by the Directors, and changes to the estimated fair value of the contingent consideration are recorded as an adjustment to goodwill or the underlying asset value.

### **Deferred taxation**

Deferred taxation is provided on timing differences which at the balance sheet date result in an obligation to pay more tax or a right to pay less tax at a future date, at rates expected to apply when they crystallize based on current tax rates and law. Deferred tax assets are recognized to the

extent that it is regarded as more likely than not that they will be recovered. Deferred tax assets and liabilities are not discounted.

### **Financial instruments**

The Group uses derivative financial instruments to hedge its exposure to fluctuations in interest and foreign exchange rates. Specifically, the Group uses interest rate swaps, forward currency contracts and currency options. Receipts and payments on interest rate swaps are recognized on an accruals basis, over the life of the swap, as an adjustment to interest payable. Gains and losses on forward currency contracts and currency options are not recognized until the period that the foreign currency exposure is recognized. Option premia are deferred in the balance sheet and recognized upon the maturity of the option agreement.

### **Future requirements**

In December 2003 the Urgent Issues Task Force issued Abstract 38; Accounting for ESOP trusts and amended Abstract 17; Employee share schemes relating to employee share ownership trusts ("ESOT"). These requirements are effective for accounting periods ending on or after June 22, 2004 and will require the shares held by the ESOT to be shown as a deduction from shareholders' funds. The charge to the profit and loss account will be the difference between the market price and the exercise price at date of grant.

In June 2002, the Council of the European Union adopted a Regulation requiring listed companies in its Member States to prepare consolidated financial statements in accordance with International Financial Reporting Standards (IFRS) from January 1, 2005. The first SkyePharma Annual Report prepared under IFRS will be for the year ending December 31, 2005.

The Group has commenced a project to convert its principal financial reporting from U.K. GAAP to IFRS.

## **2 Segmental Analysis**

SkyePharma's strategy is to be a provider of integrated drug delivery services to the pharmaceutical industry, providing a full complement of drug delivery products and services ranging from formulation and development through to commercial manufacturing. As such SkyePharma's operations represent a single business segment, pharmaceuticals, served by a range of drug delivery technologies and services.

The tables below present an analysis of turnover, (loss)/profit on ordinary activities before taxation, total assets, long-lived assets and net assets by geographical area together with an analysis of cost of sales, capital expenditure and depreciation and amortization. A breakdown of turnover and cost of sales is also presented based upon the various drug delivery products and services provided.

As there is only one business segment the totals shown in the following tables represent the total for the segment and the consolidated financial statements.



*(a) Turnover*

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>By class of business:</b>			
Pharmaceuticals			
Contract development and licensing			
Milestone payments	28,379	47,736	24,196
Research and development costs recharged	9,857	7,705	5,456
	38,236	55,441	29,652
Royalties receivable	1,468	6,751	18,701
Manufacturing and distribution	6,422	7,381	4,799
	<u>46,126</u>	<u>69,573</u>	<u>53,152</u>
<b>By location of customer:</b>			
U.K.	21,411	21,000	21,327
Europe	16,511	10,333	18,027
North America	5,482	34,047	10,289
Rest of the world	2,722	4,193	3,509
	<u>46,126</u>	<u>69,573</u>	<u>53,152</u>
<b>By location of operation:</b>			
Europe	30,268	34,449	42,503
North America	15,858	35,124	10,649
	<u>46,126</u>	<u>69,573</u>	<u>53,152</u>

*(b) Cost of sales*

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>By class of business:</b>			
Pharmaceuticals			
Contract development and licensing			
	(7,917)	(12,649)	(12,085)
Royalties payable	(572)	(1,374)	(4,707)
Manufacturing and distribution	(10,331)	(10,807)	(12,994)
	<u>(18,820)</u>	<u>(24,830)</u>	<u>(29,786)</u>

Edgar Filing: SKYEPHARMA PLC - Form 20-F

(c) (Loss)/Profit on ordinary activities before taxation

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>By class of business:</b>			
Pharmaceuticals	(9,377)	1,333	(42,983)
<b>By location of operation:</b>			
U.K.	(6,840)	(7,695)	(5,825)
Europe	6,985	7,652	(3,424)
North America	(5,244)	4,759	(30,270)
Operating (loss)/profit	(5,099)	4,716	(39,519)
Associated undertaking	(578)		
Net interest payable	(3,700)	(3,383)	(3,464)
(Loss)/profit on ordinary activities before taxation	(9,377)	1,333	(42,983)

(d) Total assets and net assets

	Total assets		Net assets	
	December 31, 2002 £'000	December 31, 2003 £'000	December 31, 2002 £'000	December 31, 2003 £'000
<b>By class of business:</b>				
Pharmaceuticals	231,906	202,305	124,270	86,265
<b>By location of operation:</b>				
U.K.	74,068	53,832	151,673	145,727
Europe	73,149	83,962	(69,489)	(70,739)
North America	84,689	64,511	42,086	11,277
	231,906	202,305	124,270	86,265

(e) Capital expenditure

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>By class of business:</b>			
Pharmaceuticals	7,646	4,352	4,392

(f) Depreciation & amortization

Year to December 31,	Year to December 31,	Year to December 31,
-------------------------	-------------------------	-------------------------

Edgar Filing: SKYEPHARMA PLC - Form 20-F

	2001 £'000	2002 £'000	2003 £'000
By class of business:			
Pharmaceuticals	9,105	12,607	12,963

F-15

## (g) Long-lived assets

	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
By location of operation:		
U.K.	36,875	44,067
Europe	58,012	53,206
North America	70,534	63,857
	165,421	161,130

**3 Other operating income**

Paul Capital Royalty Acquisition Fund provided a total of \$30 million between 2000 and 2002, in return for the sale of a portion of the potential future royalty and revenue streams from DepoDur, Xatral OD, Solaraze and DepoCyt. Paul Capital will receive 15% of the annual royalties and revenues from the stated products up to a predetermined ceiling for the period until December 31, 2014. Once the predetermined ceiling is reached, the percentage participation will fall to 3% for the remainder of the period until December 31, 2014. Income of £1.1 million (2002: £9.7 million, 2001: £6.3 million) was recognized as Other operating income under this agreement on a cost to complete basis. All of the income under this agreement has now been recognized. Royalty payments to Paul Capital of £1.0 million (2002: £Nil, 2001: £Nil) have been expensed during the year.

Under a second transaction Paul Capital provided a further \$30 million during 2002 and 2003, in return for the sale of a portion of the potential future royalty and revenue streams from nine products from the Group's drug pipeline. Paul Capital will receive between 4% and 20% of the annual royalties and revenues from the nine products up to a predetermined ceiling for the period until December 31, 2015. The 20% rate applies first and the percentage then falls, when an agreed ceiling is reached, to 12.5% until a second ceiling is reached, before falling to 4% for the remainder of the period until December 31, 2015. During 2002 and 2003 the 20% rate was reduced based on the percentage of the total \$30 million that had been provided. Income of £5.0 million (2002: £4.5 million, 2001: £Nil) was recognized as Other operating income under this agreement on a cost to complete basis. Royalty payments to Paul Capital of £2.2 million (2002: £0.7 million, 2001: £Nil) have been expensed during the year.

**4 Exceptional items**

The operating exceptional items included within administration expenses are categorized as follows:

	Year to December 31, 2003 £'000
Restructuring costs	(2,673)
Impairment of intellectual property	(2,673)
Impairment of tangible fixed assets	(1,324)
Write down of fixed asset investments	(1,599)
Settlement of licensing dispute	(1,218)
	(9,487)

## Edgar Filing: SKYEPHARMA PLC - Form 20-F

The exceptional charge includes £2.7 million relating to the reorganization of some research and development operations and other business functions, involving some staff redundancies at most sites. The reorganization is expected to be completed during 2004. A further £4.0 million is in respect of the impairment of associated intellectual property and tangible fixed assets. In addition, £1.6 million relates to a write down in value of fixed asset investments.

### 5 Operating (loss)/profit

Operating (loss)/profit is stated after charging:

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Depreciation of tangible fixed assets			
owned assets	4,343	5,616	5,704
assets held under finance leases	435	485	590
Amortization of intangible fixed assets			
amortization of goodwill	2,844	3,799	4,072
amortization of intellectual property	1,282	2,483	2,379
Research and development expenses			
current year expenditure	17,918	29,285	30,520
amortization of deferred expenditure	201	224	218
Operating lease rentals			
hire of plant and machinery	266	434	86
other	3,659	3,336	3,405

Services provided by the Group's auditor and network firms.

It is the Group's policy to employ the auditors on assignments additional to their statutory audit duties where their expertise and experience with the Group are important, principally tax advice and due diligence reporting on acquisitions, or where they are awarded assignments on a competitive basis.

During the year the Group (including its overseas subsidiaries) obtained the following services from the Group's auditor at costs detailed below:

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Audit services			
statutory audit	194	354	326
audit related regulatory reporting	160	160	145
Further assurance services	282	418	227
Tax services			
compliance services	81	86	228
advisory services	216	595	523
Other services not covered above			25
	933	1,613	1,474

Included in the analysis above are Group audit fees paid to the Group's auditor of £160,000 (2002: £194,000, 2001: £93,000) of which £13,000 (2002: £13,000, 2001: £13,000) was paid in respect of the parent company.

Edgar Filing: SKYEPHARMA PLC - Form 20-F

Also included above are fees paid to the Group's auditor in respect of non-audit services in the U.K. of £710,000 (2002: £990,000, 2001: £499,000).

**6 Employees**

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
<b>Employment costs:</b>			
Wages and salaries	(15,502)	(20,614)	(22,511)
Social security costs	(2,451)	(3,091)	(3,441)
Pension costs	(822)	(1,525)	(1,769)
	<b>(18,775)</b>	<b>(25,230)</b>	<b>(27,721)</b>

The average monthly number of persons employed by the Group (excluding Executive Directors) during the year was as follows:

	Year to December 31, 2001 Number	Year to December 31, 2002 Number	Year to December 31, 2003 Number
Pharmaceuticals	411	492	476

**Directors' Remuneration**

The tables below set out details of the Directors' emoluments for the years ended December 31, 2001, 2002 and 2003.

Year ended December 31, 2001	Fees and Salary £'000	Benefits £'000	Bonuses £'000	Total £'000
<b>Executive Directors</b>				
I R Gowrie-Smith	406	20	134	560
M Ashton	350	58	115	523
D Nicholson	180	10	70	260
	<b>936</b>	<b>88</b>	<b>319</b>	<b>1,343</b>
<b>Non-Executive Directors</b>				
Sir M G Beavis	30			30
R S Harris	28			28
Dr A N Karabelas	28			28
Dr K R Mansford	28			28
W Zeller	37			37
Dr J Gonella (to June 6, 2001)	11			11
T Howson (to November 26, 2001)	71			71
	<b>233</b>			<b>233</b>
	<b>1,169</b>	<b>88</b>	<b>319</b>	<b>1,576</b>



Edgar Filing: SKYEPHARMA PLC - Form 20-F

Year ended December 31, 2002	Fees and Salary £'000	Benefits £'000	Bonuses £'000	Total £'000
<b>Executive Directors</b>				
I R Gowrie-Smith	426	29	144	599
M Ashton	367	55	179	601
D Nicholson	189	10	92	291
	<u>982</u>	<u>94</u>	<u>415</u>	<u>1,491</u>
<b>Non-Executive Directors</b>				
Sir M G Beavis	53			53
R S Harris	51			51
Dr A N Karabelas	35			35
Dr K R Mansford	50			50
W Zeller	61			61
Dr D R Ebsworth (from April 11, 2002)	21			21
T Yamamoto (from October 30, 2002)	4			4
	<u>275</u>			<u>275</u>
	<u>1,257</u>	<u>94</u>	<u>415</u>	<u>1,766</u>
<b>Year ended December 31, 2003</b>				
	Fees and Salary £'000	Benefits £'000	Bonuses £'000	Total £'000
<b>Executive Directors</b>				
I R Gowrie-Smith	450	19		469
M Ashton	396	54	59	509
D Nicholson	220	10	44	274
	<u>1,066</u>	<u>83</u>	<u>103</u>	<u>1,252</u>
<b>Non-Executive Directors</b>				
Sir M G Beavis	53			53
R S Harris	49			49
Dr A N Karabelas	47			47
Dr K R Mansford	46			46
Dr D R Ebsworth	47			47
T Yamamoto	42			42
W Zeller (to May 28, 2003)	25			25
	<u>309</u>			<u>309</u>
	<u>1,375</u>	<u>83</u>	<u>103</u>	<u>1,561</u>

The emoluments of W Zeller include remuneration in respect of his capacity as a non-executive director of subsidiary companies amounting to an aggregate of 12,683 Swiss Francs. Benefits for M Ashton include a living allowance.

Bonus for Executive Directors includes cash payment and shares purchased under the Deferred Share Bonus Plan but excludes the value of Matching Shares, which will be provided by the Company at the end of the holding period (3 years), subject to the satisfaction of certain conditions.

Fees for Non-executive Directors include the cash amount of fees and, in 2002, the one-off additional payment of fees in shares.





**Pensions**

Contributions made to defined contribution pension schemes on behalf of the Executive Directors are set out below:

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
I R Gowrie-Smith	51	53	56
M Ashton	44	46	50
D Nicholson	23	24	28
	118	123	134

Total Directors' emoluments, excluding pension contributions, amounted to £1,560,638 (2002: £1,765,768, 2001: £1,575,775).

The Executive Chairman waived his entitlement to a bonus for the year ended December 31, 2003.

**Directors' Interests**

The following tables set out the interests of Directors (including the interests of their immediate families and persons connected with the Directors) as at December 31, 2001, December 31, 2002 and December 31, 2003. All interests are beneficial unless otherwise stated below. Interests in Ordinary Shares include shares acquired by the Executive Directors, other than Matching Shares not yet released, under the Deferred Share Bonus Plan and Share Purchase Plan.

**Number of ordinary shares**

	December 31, 2001	December 31, 2002	December 31, 2003
I R Gowrie-Smith	25,122,972	25,184,156	8,538,489
M Ashton	110,000	179,194	301,420
D Nicholson	137,000	171,381	235,489
Sir M G Beavis	172,000	210,297	210,297
R S Harris	101,500	131,083	131,083
Dr A N Karabelas		6,667	6,667
Dr K R Mansford	16,000	52,990	67,943
Dr D R Ebsworth (from April 11, 2002)		8,000	30,000
T Yamamoto (from October 30, 2002)			
W Zeller (to May 28, 2003)	55,000	91,162	
	25,714,472	26,034,930	9,521,388

In addition to the interests shown above at December 31, 2003, Mr I R Gowrie-Smith had a beneficial interest in 20,000 convertible bonds and Dr A N Karabelas had a beneficial interest in 2,000 American Depository Receipts, all issued by the Company.

## Number of "B" warrants

	December 31, 2001	December 31, 2002	December 31, 2003
I R Gowrie-Smith	19,797,143		
Sir M G Beavis	84,000		
	19,881,143		

All outstanding "B" Warrants lapsed on December 31, 2002.

## Ordinary Options over shares of 10 pence each

Directors	January 1, 2003	Granted	December 31, 2003	Exercise price	Date from which options can be exercised	Expiry date	Performance condition (see note)
I R Gowrie-Smith	1,234,568		1,234,568	81.0p	12-06-99	12-06-06	1
	575,539		575,539	69.5p	04-19-02	04-19-09	1
	1,008,313		1,008,313	80.6p	06-12-04	06-12-11	2
	1,178,022		1,178,022	72.3p	04-12-05	04-12-12	2
		1,935,484	1,935,484	46.5p	04-07-06	04-07-13	2
M Ashton	639,077		639,077	93.0p	03-31-01	03-31-08	1
	871,451		871,451	69.5p	04-19-02	04-19-09	1
	868,486		868,486	80.6p	06-12-04	06-12-11	2
	1,014,661		1,014,661	72.3p	04-12-05	04-12-12	2
		1,703,226	1,703,226	46.5p	04-07-06	04-07-13	2
D Nicholson	533,333		533,333	75.0p	04-29-99	04-29-06	1
	86,022		86,022	93.0p	03-31-01	03-31-08	1
	172,662		172,662	69.5p	04-19-02	04-19-09	1
	446,650		446,650	80.6p	06-12-04	06-12-11	2
	521,826		521,826	72.3p	04-12-05	04-12-12	2
		946,237	946,237	46.5p	04-07-06	04-07-13	2

## Super Options over shares of 10 pence each

Directors	January 1, 2003	Granted	December 31, 2003	Exercise price	Date from which options can be exercised	Expiry date	Performance condition (see note)
I R Gowrie-Smith	2,385,009		2,385,009	56.67p	05-25-04	05-25-09	3
M Ashton	2,044,293		2,044,293	56.67p	05-25-04	05-25-09	3
D Nicholson	1,022,147		1,022,147	56.67p	05-25-04	05-25-09	3

**Performance condition 1** Options granted may be exercised only if, over a period of three consecutive years, the shareholder return of the Company exceeds the growth in the FTSE All Share Index over the same period.

**Performance condition 2** Options granted vest after three years on a scale between 0% and 100% depending on the Company's performance relative to the performance of a comparator group of companies.

**Performance condition 3** Options granted may be exercised only if, over a period of five consecutive years, the shareholder return of the Company lies within top quartile growth of the FTSE 250 Share Index over the same period.

No options were exercised by any Director during the year.

Options granted were for nil consideration.

All options held by and granted to the Directors are subject to the performance conditions and terms of the SkyePharma Executive Share Option Scheme, the European and North American Scheme and the SkyePharma PLC 1999 Share Option scheme as described above.

As at December 31, 2003, none of the Directors had any interests in shares of any other Group company. The market value of Ordinary Shares at December 31, 2003 was 75.25 pence. The market value of Ordinary Shares during 2003 ranged from the lowest closing mid-price of 41.5 pence to the highest closing mid-price of 79.25 pence. The holdings of the Directors have not changed since December 31, 2003 except for the following:

#### SkyePharma PLC Share Purchase Plan

As a result of transactions on January 30, 2004, February 27, 2004, March 31, 2004 and April 30, 2004 by the SkyePharma PLC Share Purchase Plan (an Inland Revenue approved all employee share purchase plan), Michael Ashton and Donald Nicholson, Directors of the Company, as trustees of the Plan became the non- beneficial owners of an additional 21,907 Ordinary Shares of the Company. Of these shares the Directors of the Company have the following beneficial interests in Partnership Shares (Ordinary Shares of the Company) as a result of their personal participation in the Plan: Ian Gowrie- Smith: 780; Michael Ashton: 780 and Donald Nicholson: 780. In accordance with the rules of the Plan these Directors have been awarded Matching Shares (Ordinary Shares in the Company) on the basis of one Matching Share for each Partnership Share. The beneficial ownership of these Matching Shares will pass to the Directors in three years' time subject to continued employment and the retention of the underlying Partnership Shares: Ian Gowrie- Smith: 780; Michael Ashton: 780 and Donald Nicholson: 780. Partnership Shares were purchased at a price of 70, 64, 62 and 61 pence per share. Matching Shares were awarded at a price of 70, 64, 62 and 61 pence per share.

#### SkyePharma PLC Deferred Share Bonus Plan

In April 2004 the remuneration committee approved bonuses relating to the year 2003 of £59,400 and £44,000 for Michael Ashton and Donald Nicholson respectively, of which 100% of the net bonus was invested into shares in the Company, the "Executive Shares". The number of Executive Shares and conditional matching shares awarded at 59.92 pence per share on May 5, 2004, the last practicable date following the end of the company's close period, is as follows:

<b>Directors</b>	<b>Number of Executive Shares</b>	<b>Number of Conditional Matching Shares</b>
M Ashton	58,487	99,132
D Nicholson	43,324	73,431

The register of Directors' interests, which is open to inspection, contains full particulars of Directors' shareholdings and options to acquire shares in the Company.

**7 Interest Receivable**

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Interest	1,215	1,081	1,029
Share of interest receivable of associate	36		
	<u>1,251</u>	<u>1,081</u>	<u>1,029</u>

**8 Interest Payable**

	Year to December 31, 2001 £'000	Year to December 31, 2002 £'000	Year to December 31, 2003 £'000
Interest payable on bank loans, overdrafts and other loans:			