SERONO S A
Form 20-F
March 16, 2005

As filed with the Securities and Exchange Commission on March 16, 2005.

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

FORM 20-F

(Mark One)

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

or

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

For the fiscal year ended December 31, 2004

or

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

Commission File Number: 1-15096

SERONO S.A.
(Exact name of Registrant as specified in its charter)

Not Applicable	**Switzerland**
(Translation of Registrant's name into English)	(Jurisdiction of incorporation or organization)

15 bis, Chemin des Mines
Case Postale 54
CH-1211 Geneva 20
Switzerland
(Address of principal executive offices)

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

Title of each class:	**Name of each exchange on which registered:**
Bearer Shares, nominal value CHF25 per share	New York Stock Exchange*
American Depositary Shares (as evidenced by American Depositary Receipts), each representing one fortieth of a Bearer Share	New York Stock Exchange

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*Not for trading, but only in connection with the registration of American Depositary Shares, pursuant to the requirements of the Securities and Exchange Commission.

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

None

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act:

None

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of December 31, 2004.

Bearer Shares, nominal value CHF 25 per share:	10,126,741 outstanding
Registered Shares, nominal value CHF 10 per share:	11,013,040 outstanding

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.

x Yes ¨ No

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

¨ Item 17 x Item 18

Serono S.A.
Annual Report on Form 20-F
for the year ended
December 31, 2004

TABLE OF CONTENTS

The registered (®) and the filed (^{TM}) trademarks and the filed service marks (^{SM}) Canvaxin^{TM}, Cetrotide®, click.easy®, cool.click®, Crinone®, EasyJect®, Fertility LifeLines^{TM}, Ferti.net®, Fertinex®, Geref®, Gonal-f®, GHMonitor^{SM}, Howkidsgrow^{SM}, Learning for life^{TM}, Luveris®, Metrodin HP®, MSLifelines^{SM}, Mylinax ®, Novantrone®, one.click®, Ovidrel®, Ovitrelle®, Pergogreen®, Pergonal®, Profasi®, Raptiva®, Rebif®, Rebiject®, Rebiject II®, Rebiject mini®, Reliser®, Saizen®, SeroJet^{TM}, Serono®, Serophene®, Serostim®, Stilamin® and Zorbtive^{TM}, as well as the filed trademarks (^{TM}) for the "S" symbol, used alone or with the words "Serono" or "Serono biotech and beyond," are trademarks of, or are licensed to a subsidiary of, Serono S.A. Trade names and trademarks of other companies appearing in this report are the property of their respective owners.

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 Consolidated Historical Financial Data

We have derived our selected consolidated historical financial data from our consolidated financial statements. We prepare and present our consolidated financial statements in accordance with International Financial Reporting Standards or IFRS. IFRS differ in significant respects from United States Generally Accepted Accounting Principles, or U.S. GAAP. You can find a reconciliation of our audited consolidated financial statements to U.S. GAAP in Note 35 to our audited consolidated financial statements included in this Annual Report. Since the information we present below is only a summary and does not provide all of the information contained in our consolidated financial statements, you should read our consolidated financial statements and the notes to the consolidated financial statements included in this Annual Report.

	Year ended December 31,				
	2004	2003	2002	2001	2000
	(U.S. dollars in thousands, except per share data)				
Income Statement Data:					
Product sales	$ 2,177,949	$ 1,858,009	$ 1,423,130	$ 1,249,405	$ 1,146,998
Royalty and license income	280,101	160,608	114,705	127,065	92,656
Total revenues	2,458,050	2,018,617	1,537,835	1,376,470	1,239,654
Operating expenses:					
Cost of product sales	304,111	279,619	223,751	213,160	229,907
Selling, general and administrative	807,940	636,823	504,248	446,945	393,716
Research and development,	594,802	467,779	358,099	308,561	263,152
Restructuring	—	—	16,303	—	—
Other operating expense, net	227,096	199,476	85,811	70,152	31,147
Total operating expenses	1,933,949	1,583,697	1,188,212	1,038,818	917,922
Operating income	524,101	434,920	349,623	337,652	321,732
Financial income, net	63,281	44,018	36,476	51,381	52,277
Other expense, net	629	19,743	1,658	2,548	2,411
Total non-operating income, net	62,652	24,275	34,818	48,833	49,866
Income before taxes and minority interests	586,753	459,195	384,441	386,485	371,598
Taxes	90,947	68,905	63,127	69,816	70,384
Income before minority interests	495,806	390,290	321,314	316,669	301,214
Minority interests	1,653	327	536	(52)	174
Net income	$ 494,153	$ 389,963	$ 320,778	$ 316,721	$ 301,040

Per Share Data:					
Basic income per share (1)(2):					
Bearer shares	$ 32.35	$ 24.63	$ 20.07	$ 19.72	$ 19.50
Registered shares	12.94	9.85	8.03	7.89	7.80
American depositary shares (3)	0.81	0.62	0.50	0.49	0.49
Diluted income per share (1)(2):					
Bearer shares	32.29	24.59	20.04	19.68	19.46
Registered shares	12.92	9.84	8.02	7.87	7.78
American depositary shares (3)	0.81	0.61	0.50	0.49	0.49
Cash dividends paid (1)(4):					
Bearer shares	6.54	5.42	4.02	3.35	1.15
Registered shares	2.57	2.17	1.61	1.34	0.46
American depositary shares (3)	0.16	0.14	0.10	0.08	0.03
Supplemental Per Equivalent Bearer Share Data:					
Net income, basic (1)(5)	$ 32.35	$ 24.63	$ 20.07	$ 19.72	$ 19.50
Net income, diluted (1)(5)	32.29	24.59	20.04	19.68	19.46

	As of December 31,				
	2004	**2003**	**2002**	**2001**	**2000**
	(U.S. dollars in thousands, except per share data)				
Balance Sheet Data:					
Cash, cash equivalents and short- term investments	$ 1,060,978	$ 1,438,782	$ 1,064,898	$ 1,475,504	$ 1,438,485
Working capital (6)	1,183,852	1,543,933	1,139,848	1,527,359	1,505,534
Tangible fixed assets	799,878	701,453	554,509	460,767	462,425
Total assets	4,404,290	4,571,603	3,484,278	3,018,769	2,794,777
Outstanding share capital(4)	254,420	253,895	253,416	253,137	253,072
Short-term financial debts	34,527	51,224	93,598	173,254	238,585
Long-term financial debts	640,892	532,022	25,857	37,325	56,626
Shareholders' equity	2,447,878	2,880,190	2,461,198	2,218,914	2,006,416
Amounts in Accordance with U.S. GAAP:					
Net income	471,024	398,346	280,176	291,470	304,389
Basic income per share (1)(7):					
Bearer shares	30.83	25.16	17.53	18.15	19.72
Registered shares	12.33	10.06	7.01	7.26	7.89
Diluted income per share (1)(7):					
Bearer shares	30.78	25.12	17.51	18.11	19.68
Registered shares	12.31	10.05	7.00	7.24	7.87
Total shareholders' equity	2,398,311	2,855,473	2,456,683	2,239,711	2,015,860
Total assets	4,367,211	4,561,583	3,483,295	3,069,873	2,794,465
Margins and Other Data:					
Gross margin (8)(9)	86.0%	85.0%	84.3%	82.9%	80.0%
Operating margin (8)(10)	21.3%	21.5%	22.7%	24.5%	26.0%
Net margin (8)(11)	20.1%	19.3%	20.9%	23.0%	24.3%
Cash dividends paid (4)	$ 99,354	$ 85,709	$ 64,238	$ 53,759	$ 17,755
Net cash flow from operating activities	$ 471,709	$ 542,859	$ 531,982	$ 404,950	$ 255,443
Depreciation and amortization	$ 145,221	$ 135,607	$ 100,552	$ 98,906	$ 86,266
Additions to tangible fixed assets	$ 151,504	$ 185,045	$ 125,324	$ 97,131	$ 67,080
Average number of employees	4,740	4,597	4,559	4,384	4,117

	Year ended December 31,					
	2004		2003		2002	
	Sales	% Total	Sales	% Total	Sales	% Total
	(U.S. dollars in millions)					
Product sales by Region:						
Europe	$ 895.2	41.1%	$ 796.8	42.9%	$ 620.4	43.6%
North America	837.9	38.5	694.3	37.4	479.6	33.7
Middle East, Africa and Eastern Europe	196.3	9.0	151.2	8.1	107.6	7.6
Asia-Pacific, Oceania and Japan	137.5	6.3	116.9	6.3	106.3	7.4
Latin America	111.0	5.1	98.8	5.3	109.2	7.7
Total product sales	$ 2,177.9	100.0%	$ 1,858.0	100.0%	$ 1,423.1	100.0%

	Year ended December 31,					
	2004		2003		2002	
	Sales	% Total	Sales	% Total	Sales	% Total
	(U.S. dollars in millions)					
Product sales by Therapeutic Area:						
Neurology:						
Rebif	$ 1,090.6	50.1%	$ 819.3	44.1%	$ 548.8	38.6%
Novantrone	32.4	1.5	30.9	1.7	0.3	0.0
Total Neurology	1,123.0	51.6	850.2	45.8	549.1	38.6
Reproductive Health:						
Gonal-f	572.7	26.3	526.1	28.3	450.4	31.6
Cetrotide	24.8	1.1	24.8	1.3	18.4	1.3
Crinone	19.8	0.9	20.8	1.1	10.9	0.8
Ovidrel	17.7	0.8	12.4	0.7	5.7	0.4
Luveris	10.6	0.5	10.0	0.6	6.6	0.5
Core Infertility Portfolio	645.6	29.6	594.9	32.0	492.0	34.6
Metrodin HP	15.9	0.7	24.8	1.3	50.1	3.5
Pergonal	11.5	0.5	45.8	2.5	46.0	3.2
Profasi	6.7	0.3	15.4	0.9	19.8	1.4
Other products	12.6	0.7	12.0	0.6	14.0	1.0
Total Reproductive Health	692.3	31.8	692.9	37.3	621.9	43.7
Growth and Metabolism:						
Saizen	182.1	8.4	151.5	8.1	124.0	8.7
Serostim	86.8	4.0	88.7	4.8	95.1	6.7
Zorbtive	0.9	0.0	0.0	0.0	0.0	0.0
Total Growth and Metabolism	269.8	12.4	240.2	12.9	219.1	15.4
Dermatology						
Raptiva	4.9	0.2	0.0	0.0	0.0	0.0
Total Dermatology	4.9	0.2	0.0	0.0	0.0	0.0
Other products	87.9	4.0	74.7	4.0	33.0	2.3

Total product sales	$ 2,177.9	100.0%	$ 1,858.0	100.0%	$ 1,423.1	100.0%

(1) Basic and diluted per share data have been calculated net of treasury shares held on the following basis:

	Year ended December 31,				
	2004	2003	2002	2001	2000
Basic per share:					
Bearer shares	10,871,187	11,427,194	11,580,611	11,658,108	11,032,835
Registered shares	11,013,040	11,013,040	11,013,040	11,013,040	11,013,040
Equivalent bearer shares	15,276,403	15,832,410	15,985,827	16,063,324	15,438,051
Diluted per share:					
Bearer shares	10,896,618	11,452,890	11,598,155	11,687,609	11,063,889
Registered shares	11,013,040	11,013,040	11,013,040	11,013,040	11,013,040
Equivalent bearer shares	15,301,834	15,858,106	16,003,371	16,092,825	15,469,105

(2) The portion of net income allocated to bearer and registered shares was $351,655 and $142,498, respectively, for the year ended December 31, 2004, $281,459 and $108,504, respectively for the year ended December 31, 2003, and $232,381 and $88,397, respectively, for the year ended December 31, 2002. On a diluted basis, the portion of net income allocated to bearer shares and registered shares was $351,892 and $142,261, respectively, for the year ended December 31, 2004, $281,635 and $108,328, respectively for the year ended December 31, 2003, and $232,478 and $88,300, respectively, for the year ended December 31, 2002.

(3) Per share data for American depositary shares is equal to one-fortieth of the amount shown for bearer shares.

(4) Dividends for any fiscal year are generally declared and paid in the following year, after approval at the annual shareholders' meeting.

(5) Supplemental per equivalent bearer share data have been calculated on the basis of the number of total equivalent bearer shares outstanding during the applicable period, as set forth in footnote (1) above. Per equivalent bearer share information assumes the conversion of all of our outstanding registered shares into bearer shares. We believe the per equivalent bearer share information may be useful to investors in analyzing our financial results on a per share basis. Because our bearer shares and registered shares have different dividend rights, we believe that per equivalent bearer share information should be considered in conjunction with our other reported per share data in order to obtain a clear understanding of our consolidated historical per share information.

(6) Working capital means current assets less current liabilities.

(7) The portion of net income in accordance with U.S. GAAP allocated to bearer shares and registered shares was $335,196 and $135,828 respectively, for the year ended December 31, 2004, $287,510 and $110,836, respectively, for the year ended December 31, 2003, and $202,968 and $77,208, respectively, for the year ended December 31, 2002. On a diluted basis, the portion of net income allocated to bearer shares and registered shares was $335,422 and $135,602, respectively, for the year ended December 31, 2004, $287,689 and $110,657, respectively, for the year ended December 31, 2003, and $203,053 and $77,123, respectively, for the year ended December 31, 2002.

(8) These measures are not defined in IFRS or U.S. GAAP and should not be considered as an alternative to any IFRS and U.S. GAAP data. The method of calculating these measures may be different from methods used by other companies.

(9) Gross margin means gross profit divided by product sales. Gross profit means product sales less cost of product sales.

(10) Operating margin means operating income divided by total revenues.

(11) Net margin means net income divided by total revenues.

Risk Factors

We operate in a rapidly changing environment that involves a number of risks, some of which are beyond our control. You should carefully consider each of the risks and uncertainties we describe below and all of the other information in this Annual Report before deciding to invest in our bearer shares or ADSs. The risks and uncertainties we describe below are not the only ones facing our company. Additional risks and uncertainties that we do not currently know or that we currently believe to be immaterial may also adversely affect our business.

Risks Related to Technological Change and Research and Development

If technological change makes our products obsolete, we will no longer be able to sell our products and our revenues will decline

Pharmaceutical and biotechnology development is characterized by significant and rapid technological change. Research and discoveries by others, including possible developments of which we are not currently aware, may make our products and those from which we derive royalty income obsolete. If technological changes make our products obsolete, doctors will be less likely to prescribe our products, and sales of our products will be reduced. If sales of our products are reduced, our results of operations could be adversely affected.

If we are not able to develop and realize the full market potential of our current and new products, we may not be able to maintain our current level of sales growth and our stock price could decline

Our long-term growth will depend on our ability to realize the full market potential of our current products and to develop and commercialize new products. Successful biotechnology product development is highly uncertain and depends on numerous factors, many of which are beyond our control. We currently have approximately 30 post-discovery projects in preclinical or clinical development. Products that appear promising in the early phases of development may fail to reach the market for numerous reasons, including, but not limited to:

- development of products may be stopped due to a variety of reasons, such as lack of efficacy, harmful side effects and evolution of the competitive environment. For example, in July 2004, the development of emfilermin in embryo implantation failure was stopped due to inadequate efficacy in a Phase II clinical trial;

- we may not successfully complete clinical trials for our products within any specific time period, or at all, for a variety of reasons, such as our inability to attract a sufficient number of investigators, our inability to enroll and maintain a sufficient number of patients in the clinical trials and suspension of the trials by regulatory authorities;

- products may fail to receive necessary regulatory approvals. For example, in April 2003 the Committee for Proprietary Medicinal Products recommended not granting marketing authorization for our high-dose recombinant human growth hormone product, Serostim, for the treatment of AIDS Wasting in the European Union;

- products may turn out to be uneconomical to commercialize because of manufacturing costs or other factors.

These factors are important, not only with respect to new drugs, but also with respect to new indications for existing drugs, because we must obtain regulatory approval for each indication and market acceptance for various indications may vary. These factors may also lead to gaps in the product development pipeline and delays between the approval of one product and approval of the next new product.

Risks Related to Our Products and Markets

If we encounter problems with any of our key suppliers or service providers, we could experience higher costs of sales, delays in our manufacturing or loss of revenues

Other companies produce raw materials necessary for the manufacture of some of our products, as well as some of our products themselves. As a result, we are subject to the risk that some of the products we sell may have manufacturing defects that we cannot control. For example, we obtain Crinone exclusively from Columbia Laboratories. In April 2001, we announced a voluntary recall of batches of Crinone due to a manufacturing defect and suspended sales for the remainder of 2001 and the first part of 2002.

In some cases, we cite our third party sources specifically in our drug applications with regulatory authorities and accordingly we must obtain those materials or products as specified. We also use subcontractors for certain services, and in some cases the subcontracts are with sole- or limited-source suppliers. For example, Owen Mumford is the exclusive provider of the injection device Rebiject for use with Rebif, our largest product. Our subcontractors may also be registered with the regulatory authorities, so we would have to obtain regulatory approval in order to use a different subcontractor. If such services were no longer available at a reasonable cost from those suppliers, we would need to find new subcontractors.

If our suppliers experience manufacturing defects or if we have to find and register alternative raw material, product or service suppliers, we may experience significant delays in our ability to manufacture or sell our products and incur significant expense or fail to realize significant revenues.

We may encounter unexpected difficulties in the design and construction of production facilities and the scale-up of production to viable commercial levels

In order to manufacture a product candidate commercially, we require access to large-scale production facilities. We may encounter unexpected difficulties in the design and construction or adaptation of production facilities and the scale-up of production to viable commercial levels. These difficulties could result in substantial additional costs or affect the commercial viability of a product candidate. We are particularly at risk of encountering these difficulties in the manufacture of biological products, which are inherently more difficult to produce than chemical compounds.

We face growing and new competition that may reduce our likelihood of market success

We operate in a highly competitive environment. This competition may become more intense as commercial applications for biotechnology products increase. Our principal competitors are pharmaceutical companies, pharmaceutical divisions of chemical companies and biotechnology companies. Some of our competitors have greater clinical, research, regulatory, financial and marketing resources than we do and may be able to market competing products earlier than we do or market products with greater efficacy, fewer side effects or lower cost than ours. For example, the approval and launch of natalizumab (Tysabri) in the United States by Biogen Idec and its partner Elan in November 2004 is an indication of increasing competition in the field of multiple sclerosis.

Small biotechnology companies, academic institutions, governmental agencies and other public and private research organizations conduct a significant amount of research and development in the biotechnology field. These entities may seek patent protection and enter into licensing arrangements to collect royalties for the use of technology they have developed. We face competition in licensing activities from pharmaceutical companies, pharmaceutical divisions of chemical companies and biotechnology companies that also seek to acquire technologies from the same entities. If we are not able to compete effectively with these entities to acquire the technology we need to develop new products, we may not be able to maintain our current level of sales growth and our stock price could decline.

We may be required to revise the labeling for our products from time to time

We may be required to change the labeling for our products for a variety of reasons, such as to include new safety or efficacy data from clinical trials or post-marketing surveillance, to reflect experiential use following a period of commercialization, or to be in keeping with evolving regulatory or clinical environments. Prescribers of our products may interpret such changes in various ways that could influence their decisions on initiation, further use or discontinuance of these products. If prescribers interpret changes in the labeling of our products in ways that cause them to decrease or cease prescribing those products, we may not be able to continue our current level of sales growth and our stock price could decline.

Resale of our biotechnology products within the European Union may cause our sales and gross profit margin to decline

In an effort to create a single economic sphere and reduce barriers to the mobility of commercial products, the European Union has interpreted its competition and patent laws to permit the resale of various products, including biotechnology products. In 2004, $895.2 million (41.1%) of our product sales were in Europe. Once we place our products in the stream of commerce in the European Union, we have limited ways of preventing third-party distributors from re-packaging, and then reselling, our products in any other country of the European Union. However, our prices vary across the European Union, principally as a function of different government policies regarding product pricing and reimbursement. Third-party distributors may purchase our products in markets within the European Union where our prices are lower, and then re-sell our products in countries where prices are higher. As a result, we face competition from third-party distributors that resell our products into these latter countries. We do not have the right to be the exclusive seller of our products within the European Union, nor do our patent rights protect us from third-party distributors re-selling our products in this manner. As a result, we cannot prevent a shift in sales to markets in which we realize lower unit sales prices for our products. If we sell a larger percentage of our products into these markets, our sales and gross profit margin will decline. We bear a similar risk to the extent that our products may be imported into the United States from Canada.

Competition from non-approved uses and generic drugs could reduce our sales growth

We face competition from generic products and products sold for non-approved uses. For example, Serostim faces competition from drugs prescribed for non-approved indications. Physicians may prescribe anabolic steroids or competing human growth hormone products to treat AIDS Wasting although, as indicated by their labeling, regulators have not approved these products for this indication. In addition, producers of generic products may receive approval for the sale of their drugs by relying on the registration files of products already granted regulatory approval. Because producers of generic products do not have to incur the costs necessary to go through the full drug development process to prove that their products are safe and effective for these indications, they can afford to sell their products at lower prices than products like ours which have gone through that process. It is possible that our products will lose market share to these alternative therapies and that therefore we may not be able to maintain our current level of sales growth and our stock price could decline.

We may also face competition from the introduction of biosimilar products in Latin America and in Asia. These are not generic versions of Rebif as the exact formulation for Rebif is highly dependent on our well-established manufacturing process. In the United States and in Europe, regulatory agencies have so far recognized the need for clinical testing of biosimilar products to establish both efficacy and safety. However, in Latin America (Mexico and Argentina) licenses for biosimilar products were granted in the fourth quarter of 2004. Although biosimilar products are not proven and supply may be restricted, we expect there will be some impact on Rebif sales in these regions.

Sales of counterfeit products may damage our reputation and cause customers to lose faith in our products

As a manufacturer of biotechnology products, we are subject to the risk that third parties will attempt to create counterfeit versions of our products and sell the counterfeits as our products. For example, in January 2001 and again in May 2002, we discovered that a counterfeit product was being sold as Serostim in the United States. Counterfeit products are not approved by regulatory authorities and may not be safe for use. If any counterfeit products are sold as ours, our reputation could suffer and patients could lose faith in our products. In addition, our products could be subject to recall in the event of counterfeit sales. If patients lose faith in our products or we are forced to recall any of our products as a result of the counterfeiting of those products, our sales could decline.

Risks Related to Our Sources of Revenue

If our sales of any of our major products decline, our profitability would be reduced

In 2004, Rebif, our recombinant beta interferon, accounted for 50.1% ($1,090.6 million) of our total product sales. Rebif faces competition from Avonex and Betaseron, other recombinant beta interferon products, from Copaxone (glatarimer acetate), another drug used in multiple sclerosis, and from Tysabri (natalizumab). Because our business is highly dependent on Rebif, a reduction in revenue from sales of Rebif would have a significant impact on our overall profitability. Further, in 2004, Gonal-f, our recombinant follicle stimulating hormone, accounted for 26.3% ($572.7 million) of our total product sales. Gonal-f faces competition from Puregon (marketed in the United States as Follistim), another recombinant product, and a variety of other FSH products. Because our business is highly dependent on Gonal-f, a reduction in revenue from sales of Gonal-f would have a significant impact on our overall profitability.

Our revenues are dependent on reimbursement from third-party payers who could reduce their reimbursement rates

In most of our markets, sales of our products are or may be dependent, in part, on the availability of reimbursement from third-party payers. These payers include state and national governments, such as the health systems in many European Union countries and Medicaid and Medicare programs in the United States, and private insurance plans.

When a new product is approved, the reimbursement status and rate for the product is uncertain and must be negotiated with third-party payers in each European country, a process that can take up to several years. In addition reimbursement policies for existing products may change at any time. Changes in reimbursement rates or our failure to obtain and maintain reimbursement for our products may reduce the demand for, or the price of, our products and result in lower product sales or revenues. For example, in January 2004 the Federal Republic of Germany, Europe's largest pharmaceutical market, announced an across-the-board reduction of 10% in reimbursement rates for all pharmaceuticals, including our products.

In certain markets, the pricing and reimbursement of our products are subject to government controls. In Europe, some third-party payers link the reimbursement price to maximum quantities of the product sold in a given year. Single payer medical insurance systems, which are predominant in Europe, are under increasing financial strain, which creates an incentive to decrease the amount that such systems will pay to reimburse the cost of drugs. In the United States, there have been, and we expect there will continue to be, a number of state and federal proposals that limit the amount that state or federal governments will pay to reimburse the cost of drugs, and we believe the increasing emphasis on managed care will put pressure on the price and usage of our products, which may impact product sales. For example, in 2001 and 2002 many states in the United States imposed prior authorization requirements for the purchase of certain drugs under Medicaid, including Serostim. Not all jurisdictions recognize the importance of infertility treatment and accordingly do not offer reimbursement coverage for such treatment. In addition, in some countries the extent of reimbursement may be affected by local public policy and ethical concerns about certain therapies, such as in vitro fertilization.

Third-party insurance coverage may not be available to patients for products we discover and develop. If third-party payers do not provide adequate coverage and reimbursement levels for our products, the market acceptance of these products may be significantly reduced.

We may have difficulty successfully integrating acquired businesses with our operations

From time to time, we may acquire businesses. We may not be able to successfully implement integration plans, dispose of certain non-core businesses, or profitably manage those businesses. We may not realize the expected synergies of acquisitions.

A significant percentage of our net income is dependent on royalty and license payments that are beyond our control

We derive a significant percentage of our net income from royalty and license income. Our royalty and license income was $280.1 million in 2004 and $160.6 million in 2003, relating primarily to royalties received from Biogen Idec on its sales of Avonex, Organon on its sales of Puregon, Amgen (formerly Immunex) on its sales of Enbrel, and Abbott on its sales of Humira. In addition to ongoing royalty payments, we also receive periodic milestone payments and other revenues pursuant to contracts related to our intellectual property. Our receipt of these payments is largely dependent on the successful development and sale of products by other companies over which we have no control or against which we compete. In addition, some of these revenues are dependent on patents that may be invalidated or expire. If these parties are not successful at developing and selling their products or our underlying patents are no longer in force, our net income could decline.

Our investment income is unpredictable and the value of our investments may decline in the future

Our financial assets include deposits with prime banks, investments in short-term money market funds and rated bonds with a life to maturity of up to three years. The income generated by these assets is sensitive to movements in interest rates and, in the case of the rated bonds, the realizable value of the investment also can be influenced by movements in the market price related to the underlying asset. For example, a decrease in short-term U.S. dollar interest rates would have a direct impact on the revenue generated by our bank deposits and money market funds. An increase in longer-term interest rates would negatively impact the fair value of our longer-term bond investments. Similarly, a rating downgrade or change in the market's perception of risk can lead to a reduction in the fair value of our bond investments. For example, our 2003 net financial income ($36.9 million) was lower than our 2002 net financial income ($54.0 million) due to a low interest rate environment and the maturity during the latter period of longer-term bond investments with higher rates of interest. Although our 2004 net financial income ($44.1 million) was higher than in 2003, we cannot predict how interest rates and other factors that affect net financial income will change in the future. For example, if interest rates continue to stay low or fall further, our net

financial income may be reduced when compared to previous periods.

We have a number of minority participations in listed and unlisted companies that are usually, but not always, related to collaborative agreements with the respective company. The value of the unlisted investments can be difficult to assess, and changes in the market value of the listed investments can have an impact on our income. For example, in the fourth quarter of 2003, we took a non-cash charge of $16.1 million related to the write-down of our equity investment in Swiss International Air Lines.

Foreign exchange fluctuations could significantly impact the U.S. dollar value of our revenues and expenses

Our operations are conducted by subsidiaries in many countries, and the results of operations and the financial position of each of those subsidiaries are reported in the relevant currency and then translated into U.S. dollars at the applicable exchange rate for inclusion in our consolidated financial statements. As a result, our reported sales figures may differ substantially from our sales figures as measured in local currencies. For example, in 2004 our sales growth was 11.5% in local currencies, but 17.2% as reported in U.S. dollars. Due to this translation effect, the prevailing foreign exchange rate could cause our sales growth rates to not meet expectations. If our sales figures do not meet market expectations, our stock price could decline.

Conversely, our reported expenses may also differ substantially from our expenses as measured in local currencies. For example, in 2004 our expenses growth was 22.1% as reported in U.S. dollars, but 16.3% in local currencies. Due to this translation effect, the prevailing foreign exchange rate could cause our net income growth rate to not meet expectations. Again, if our sales figures do not meet market expectations, our stock price could decline.

Risks Related to Government Regulation

Governmental regulations may restrict our ability to sell our products, which could result in a loss of revenues and a decrease in our stock price

Our research, preclinical testing, clinical trials, facilities, manufacturing, labeling, pricing, and sales and marketing are subject to extensive regulation by numerous governmental authorities, including authorities in the European Union (such as the European Medicine Agency or EMEA) and Switzerland, as well as governmental authorities in the United States, such as the Food and Drug Administration, or FDA. Our research and development activities are subject to laws regulating such things as laboratory practices and the use and disposal of potentially hazardous materials including radioactive compounds and infectious disease agents. We are also required to obtain and maintain regulatory approval to market products for approved indications in the European Union, the United States, Japan and other markets. Obtaining regulatory approval is a lengthy and complex process. For example, though we have obtained regulatory approval to sell Gonal-f in 95 countries including the United States and the countries of the European Union, in order to obtain regulatory approval to sell the product in Japan we have been required to conduct additional local clinical studies, which will delay potential registration of Gonal-f in this market. Even if we are able to obtain regulatory approval for our products, both our manufacturing processes and our marketed products are subject to continued review. Later discovery of previously unknown problems with the safety or efficacy of our products or manufacturing processes may result in restrictions on these products or processes, including withdrawal of the products from the market or suspension of our manufacturing operations. For example, in February 2003, the Committee on Safety of Medicines advised that Metrodin HP should no longer be used in the United Kingdom. The Committee based its advice on the precautionary principle that products manufactured from human urine sourced from a country with one or more cases of variant Creutzfeldt-Jakob Disease, or vCJD, should not be used whenever practicable. Metrodin HP was manufactured from urine sourced from Italy, and the withdrawal of Metrodin HP from the United Kingdom market was a precautionary measure following the confirmation of a case of vCJD in Italy. In February 2005, the United States Department of Health and Human Services announced the establishment within the FDA of a new Drug Safety Oversight Board to monitor FDA-approved medicines once they are on the market and update physicians and patients with emerging information on risks and benefits. Any adverse report by this Board with respect to our products could have an effect on our product sales, profits and stock price.

Pharmaceutical usage guidelines may recommend lower use of our products

If government agencies or other respected groups or organizations recommend reducing the use of one of our products, our sales of that product could drop and our revenues could be reduced. In addition, professional societies, practice management groups, private foundations and organizations involved in various diseases may also publish

guidelines or recommendations to the health care and patient communities. These organizations may make recommendations that affect a patient's usage of certain therapies, drugs or procedures, including our products. Such decisions may also influence prescription guidelines for our products issued in other countries. Recommendations or guidelines that are followed by patients and health care providers could result in, among other things, decreased use of our products. For example the National Institute for Clinical Excellence (NICE) in the U.K. systematically issues guidelines in selected therapeutic areas which may limit prescription of our products.

Potential regulation of the use of biological materials could make production of our products more expensive or not possible

We use biological materials, in particular animal-derived materials, in the development and manufacture of our products. Some interest groups in the European Union and the United States are seeking to ban or regulate the use of animal-derived materials generally, including their use in biotechnology products and for research and development.

Although we are developing manufacturing processes for our major molecules that will be free of animal-derived components, we may not be successful in that development and we cannot be certain that regulatory authorities will approve the new processes. If a government were to ban or regulate our use of animal-derived materials, we would incur additional costs that could make the production of our products less profitable or economically impractical, or we could have to cease production of certain of our products, which could cause our net income and stock price to decline.

Risks Related to Legal Uncertainty

If we are not able to defend our intellectual property rights, we may lose the competitive advantage they give us

Our long-term success depends largely on our ability to market technologically competitive products. The patents and patent applications relating to our products and the technologies from which we derive license revenue may be challenged, invalidated or circumvented by third parties and might not protect us against competitors with similar products or technology. Any challenge to or invalidation or circumvention of patents related to products produced using licenses we have granted could affect our licensing revenues. If we are unable to prevent unauthorized third parties from using proprietary rights relating to our products, we will not be able to realize the full value of our research investment, and we will lose a source of competitive advantage. Even if our patents are not invalidated or circumvented, each of them will eventually expire.

The competitive position of a number of our products is dependent on various patents. We believe that these patents discourage other companies from entering our markets. Certain of these patents also allow us to realize licensing revenue from competitors whose products would otherwise infringe these patents. If we cannot defend these patents, other companies could sell products that directly compete with our products.

Moreover, the patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual issues. Important legal issues remain to be resolved as to the extent and scope of available patent protection for biotechnology products and processes in the European Union, the United States and other important markets. To date, no consistent policy has emerged regarding the breadth of claims allowed in pharmaceutical and biotechnology patents. As a result, it is difficult for us to assess the amount of protection our patents provide for our competitive position.

We rely on trade secrets and trademarks to protect our technology, especially where we believe patent protection not to be appropriate or obtainable. We protect our proprietary technology and processes, in part, by confidentiality agreements with our key employees, consultants, collaborators and contractors. These agreements may be breached, or we may have inadequate remedies for any breach, or our trade secrets or those of our collaborators or contractors may otherwise become known to or be discovered independently by competitors.

If we do not have access to the intellectual property we need for our business, our ability to develop and market our products may be limited

We are aware that others, including various universities and companies working in the biotechnology field, have filed patent applications and have been granted patents in the European Union, the United States and other jurisdictions claiming subject matter potentially useful or necessary to our business. Some of those patents and applications claim only specific products or methods of making such products, while others claim more general processes or techniques useful or now used in the biotechnology industry, either alone or in combination with other products. For example, Berlex Laboratories and Schering AG own three U.S. patents that they have asserted cover the recombinant manufacture of interferon beta. Following the filing by us of a declaratory judgment action against Berlex and Schering AG asserting that we do not infringe their patent rights, we settled with them and agreed to make a one-time payment to Berlex and pay Berlex royalties on our U.S. sales of Rebif in the United States for a limited period of time.

Litigation and administrative proceedings, which could result in substantial costs to us, may be necessary to enforce any patents issued to us or to determine the scope and validity of third-party proprietary rights. We have in the past been, are currently, and may in the future be involved in patent litigation. If we lose one of these proceedings, we may be required to obtain third-party licenses at a material cost or cease using the technology or product in dispute. If others have or obtain patents or proprietary rights with respect to products we currently are developing, we may not be able to continue to research and develop our products profitably. If we are unable to enforce our patents, we may lose competitive advantage or marketing revenue.

If we are subject to significant legal action or to a government investigation, we may incur substantial costs related to pursuing or settling such litigation or investigation

We participate in an industry that has been subject to significant product liability, intellectual property and other litigation and to government investigations. Many of these actions involve large claims and significant defense costs. For example, our principal U.S. subsidiary has received subpoenas from the U.S. Attorney’s office in Boston, Massachusetts, relating to Serostim. The outcome of this investigation could include the imposition of substantial civil and/or criminal penalties that could be material to us, including exclusion from government reimbursement programs. For a further description of this matter, please see “Item 8—Legal Proceedings.”

Changes in tax laws could adversely affect our earnings

Changes in the tax laws of Switzerland, the United States or other countries in which we do significant business, as well as changes in our effective tax rate for the fiscal year caused by other factors, could affect our net income. During 2004, no major tax legislation was enacted that would materially impact our net income. It is not possible to predict the impact on our results of any tax legislation that may be enacted in the future.

Risks Related to Our Share Price and Corporate Control

Our share price is likely to be volatile and may decline

The market price for our shares has been volatile and may continue to be volatile in the future. During 2004, based on prices on the virt-X, our bearer share price ranged from CHF 711 to CHF 974. During the same period, based on prices on the New York Stock Exchange, the price range for our ADSs ranged from $14.57 to $19.60. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of the shares and may cause the price to decline:

Ÿa revenue shortfall, which, due to fixed near-term expenses, causes a period’s results to be below expectations;

- Ÿ a short-term increase in expenses that is not matched by a corresponding increase in revenue;
- Ÿ changes in wholesaler buying patterns;
- Ÿ publicity regarding our collaborations and actual or potential results relating to products and indications under development by us or our competitors;
- Ÿ regulatory developments in the countries in which we operate;

- Ÿ public concern as to the safety of our products;
- Ÿ perceptions as to the prospects of our company;
- Ÿ perceptions as to the prospects of our competitors and the biotechnology industry in general;
- Ÿ general market conditions;
- Ÿ changes in the exchange rate of the U.S. dollar against the euro and the Swiss franc; and
- Ÿ period-to-period fluctuations in our financial results.

The value of dividends on our ADSs will be affected by exchange rates

We declare and pay dividends on our bearer shares in Swiss francs. Exchange rate fluctuations between the Swiss franc and the U.S. dollar will affect the U.S. dollar value of dividends that holders of our ADSs will receive.

Our controlling shareholders may have interests that are adverse to yours

As of December 31, 2004, Bertarelli & Cie held 51.43% of our capital, including treasury shares, and 65.36% of our voting rights. Ernesto Bertarelli, our Vice Chairman, Managing Director and Chief Executive Officer, controls Bertarelli & Cie. In addition, Maria-Iris Bertarelli, Ernesto Bertarelli and Donata Bertarelli Späth own as individuals in the aggregate 7.00% of our capital, including treasury shares, and 10.53% of our voting rights. The members of the Bertarelli family may in the future, through open market purchases or otherwise, acquire additional shares. Ernesto Bertarelli, through his control of Bertarelli & Cie and his ownership of additional shares, currently controls the management of our company and the outcome of all actions requiring the approval of our shareholders. The interests of Ernesto Bertarelli and the Bertarelli family may conflict with the interests of our other investors, and you may not agree with the actions they take. For example, Mr. Bertarelli and the Bertarelli family have the combined voting power necessary to reject any offer to acquire us, even if the offer would be attractive to our other investors. In addition, Mr. Bertarelli and the Bertarelli family control enough votes that they can cause us to increase our share capital, change our corporate purposes and create shares with privileged voting rights. This could have the effect of diluting the voting rights and ownership of our other investors and of maintaining the control of Mr. Bertarelli and the Bertarelli family.

Future sales by current shareholders could cause the price of our shares to decline

If our existing shareholders sell a substantial number of our shares in the public market, the market price of our shares could fall. Subject to applicable Swiss law, United States federal securities laws and other applicable laws, the Bertarelli family may sell or distribute any and all of the shares owned by them. Sales or distributions by the Bertarelli family of substantial amounts of our capital stock, or the perception that such sales or distributions could occur, could adversely affect prevailing market prices for our shares. The Bertarelli family is not subject to any contractual obligation to retain its controlling interest.

It may not be possible to enforce judgments of United States courts against the members of our board of directors

We are a Swiss stock corporation. Most of our directors are not residents of the United States. In addition, a substantial portion of our assets and the assets of our board members are located outside the United States. As a result, it may not be possible to effect service of process within the United States on us or on our directors, or to enforce against them judgments obtained in the United States courts based on the civil liability provisions of the securities

laws of the United States. In addition, awards of punitive damages in actions brought in the United States or elsewhere may be unenforceable in Switzerland.

U.S. persons may not be able to participate in some of our securities offerings

United States securities laws may restrict the ability of U.S. persons who hold our ADSs from participating in certain rights offerings, share dividends or other transactions involving our securities that we may undertake in the future. We are not under any obligation to register any such transactions under the U.S. securities laws.

Our actual results may differ from forward-looking statements that we make in this annual report

Many statements made in this Annual Report under Items 3, 4 and 5 and elsewhere are forward-looking statements relating to future events and/or future performance, including, without limitation, statements regarding our expectations, beliefs, intentions or future strategies that are signified by the words ‘‘expects,’’ ‘‘anticipates,’’ ‘‘intends,’’ ‘‘believes,’’ “plans” or similar language. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of, among other factors, the factors set forth in this “Risk Factors” section.

We caution you that these forward-looking statements, which may deal with subjects such as our research and development plans, our marketing strategies, our planned regulatory approvals, our planned relationships with our research collaborators, the development of our business, the markets for our products, our anticipated capital expenditures, the possible impacts of regulatory requirements and other matters that are not historical facts, are only predictions and estimates regarding future events and circumstances. All forward-looking statements included in this document are based on information available to us on the date of this Annual Report, and we undertake no obligation to update these forward-looking statements to reflect events occurring after the date of this Annual Report. You should carefully consider the information set forth in this section in addition to the other information set forth in this Annual Report before deciding whether to invest in our bearer shares or ADSs.

Item 4. INFORMATION ON THE COMPANY

Overview

We are the third largest biotechnology company in the world based on 2004 total revenues of $2,458.1 million. Biotechnology companies use human genetic information to discover and manufacture therapeutic products for the treatment of human diseases. We currently focus on the highly specialized markets of reproductive health, neurology, growth and metabolism, where we have established strong positions, and on the dermatology market, which we entered, in 2004. We have a global presence with operations in over 40 countries, five principal production facilities located in four countries, sales in over 90 countries and 4,902 employees.

As a biotechnology company, research and development are central to our efforts to grow our business. We currently employ 1,387 research and development personnel, and in 2004 we spent $594.8 million on R&D. Our in-house R&D capabilities, which span a variety of disciplines, and our numerous external collaborations enhance our ability to develop new medications. We currently have approximately 30 high priority projects in preclinical or clinical development.

We have integrated operations that allow us to manufacture and market the products we derive from our R&D efforts. The use of biotechnology techniques has allowed us to improve our manufacturing efficiency and helped us to increase our product gross margin to 86.0% in 2004 from 67.7% in 1995 and to increase our net margin to 20.1% of revenues in 2004 from 4.2% in 1995.

Our 2,084 sales and marketing personnel sell our products primarily by calling on prescribing physicians in our highly specialized markets.

We are a Swiss corporation, with our principal executive offices in Geneva. We were incorporated in 1987, and our bearer shares have been listed in Switzerland since that time. Our American depositary shares or ADSs have been listed on the New York Stock Exchange since July 2000.

Our principal offices are operated by our wholly owned subsidiary, Serono International S.A., and are located at 15 bis, Chemin des Mines, Case Postale 54, CH-1211 Geneva 20, Switzerland. Our telephone number is +41-22-739-3000. We have established a Website at www.serono.com. The information on our Website is not part of this Annual Report.

Recombinant Technology

We currently market eight recombinant products— Rebif, Gonal-f, Saizen, Serostim, Ovidrel, Luveris, Zorbtive and Raptiva. Recombinant DNA technology gives us an efficient, cost-effective and consistent method of producing commercial quantities of proteins.

Proteins are important components of human cells and have various biological functions, and some proteins have been developed as therapeutics. Historically, we obtained proteins relevant to our therapeutic areas by extracting them from natural sources, such as human urine or pituitary tissue, and then purifying them. These processes have presented several challenges in terms of identifying suitable sources and economically collecting a sufficient amount of the raw materials for production.

Using recombinant technology, we now clone, or copy, the human gene containing instructions for the synthesis of a protein product and transfer it to a host cell. We then induce the host cell to produce commercial quantities of that protein. When using recombinant technology to produce pharmaceuticals, the choice of host cell is important. Recombinant DNA technology can be used to transfer genetic information into bacterial, yeast, mammalian or other

cell types. If bacterial, yeast and certain other cells are used for recombinant drug production, certain complex protein molecules may not be able to be produced in their natural forms, rendering the molecules unstable, or biologically less active or even inactive. However, mammalian host cells can produce molecules as they are made in the natural environment. All of our recombinant products are currently produced using mammalian cell technology.

Recombinant technology allows us to solve many of the problems associated with production of complex pharmaceuticals through extraction from natural sources. Because of the nature of recombinant production, we can closely control the quality and purity of the products and more easily achieve batch-to-batch consistency. In addition, we are not as dependent on difficult-to-organize raw material supply chains, so we are able to more quickly respond to changes in market demand for our products.

Neurology

Multiple sclerosis, or MS, is a chronic and often progressive debilitating disease of the central nervous system that primarily affects young adults. It is an autoimmune disease in which the body's immune system reacts against its own cells, thereby destroying the myelin sheath that protects the axons in the central nervous system. Damage to the myelin sheath impedes the normal transmission of nervous impulses. These interruptions of transmission cause motor and sensory difficulties. The progress of the disease is highly variable. However, in its most severe forms, MS leads to rapidly progressive disability and death.

Over one-half of the world's estimated 1.2 million people with MS suffer from the relapsing-remitting form of this disease, or RRMS, and nearly 80% of all MS cases start with RRMS.

RRMS patients suffer from relapses or exacerbations, which are unpredictable occurrences of new symptoms or worsening of old symptoms punctuated by remissions. In the majority of cases patients progress from RRMS into secondary progressive MS, or SPMS, as they start to accumulate disability. In the early stages of SPMS patients continue to have relapses and, together with RRMS patients, are sometimes described as having relapsing MS, or RMS. Additionally patients in the early stages of the disease, prior to a diagnosis of RRMS, may also sometimes be classified as having RMS.

We estimate that the treatment of relapsing MS with disease modifying drugs was an approximately $4.4 billion global market in 2004, based on publicly reported sales data for our product and four competing products.

Products

Rebif

Rebif is a recombinant interferon beta-1a that helps strengthen the body's immune system. It is identical to the interferon beta that the human body produces in certain circumstances, for example, in response to viral infection. Interferons fight viruses, inhibit cell multiplication and regulate the activity of the immune system. Because of their complex effects on the immune system, interferons may have important therapeutic potential in other indications.

We developed Rebif for the treatment of MS, and we currently manufacture and market it for use in the RRMS and RMS indications. In 2004, Rebif was our largest selling product, accounting for $1,090.6 million (50.1%) of total product sales. We began marketing Rebif in the United States in March 2002. In 2004, our estimated market share in the United States in terms of total prescriptions was 16.4% and 18.6% in new prescriptions.

In November 1998, we published the results of the Prevention of Relapses and Disability with Interferon beta-1a Subcutaneously in Multiple Sclerosis, or PRISMS, study in the *Lancet*. The study showed that Rebif is the first therapeutic agent to demonstrate efficacy on all major endpoints in MS (disability, relapses, MRI area and activity). In this study, 560 RRMS patients were given one of two doses of Rebif or a placebo. The results of the trial showed that Rebif reduces the number of relapses experienced by patients and delays the rate at which patients become disabled (as measured by a confirmed 1-point Expanded Disability Status Scale, or EDSS, progression). In addition, brain scans showed that the number of multiple sclerosis lesions is reduced by Rebif (as measured by a reduction in the T2 disease burden).

In June 2001, four-year data from the study were published in *Neurology* and showed that the higher of the two doses tested (44 mcg three times per week) was associated with better efficacy than the lower dose (22 mcg three times per week). In the first quarter of 2001, the European Union granted marketing approval for the highest available dose of Rebif as a first line therapy for patients with RRMS.

This research has since been followed by the publication of the Secondary Progressive Efficacy Clinical Trial of Rebif in MS, or SPECTRIMS study, in the June 2001 issue of *Neurology*. This study suggests that the rate of progression of disability in patients is reduced if Rebif is administered in the early stages of secondary progressive multiple sclerosis (in patients who continue to experience relapses) as opposed to later stages of the disease.

During 2001, we completed a study involving 677 patients in a head-to-head trial comparing the high dose of Rebif with the standard dose of our competitor's product, Avonex. The Evidence for Interferon Dose-effect: European-North American Comparative Efficacy Study, or EVIDENCE, was at the time the largest prospective comparative study of two disease-modifying drugs in MS. The objective of the study was to compare the clinical benefit of Rebif and Avonex based on pre-defined FDA-approved endpoints. We conducted the study with the concurrence of the FDA regarding its design, primary and secondary endpoints and the prospectively defined statistical analysis plan. The study showed that 32% fewer patients treated with Rebif had relapses compared to patients treated with Avonex during a six-month treatment period. In March 2002, the FDA approved Rebif on the basis that it had been shown to be clinically superior in the reduction of exacerbations at 24 weeks. 48-week data from the EVIDENCE study showed that 62% of patients who received Rebif did not have a relapse compared to 52% of Avonex-treated patients. Rebif patients had a 19% relative increase in remaining free of relapses over the 48 weeks compared to Avonex patients. Rebif patients also had a 30% reduction in the rate of occurrence of first relapse during 48 weeks relative to Avonex patients. The 12-month data from the EVIDENCE study, which showed the superiority of Rebif 44 mcg three times per week over Avonex 30 mcg once per week in reducing exacerbations, were published in the November 2002 issue of *Neurology.*

In May 2003, we and Pfizer announced that the final 63-week findings from the EVIDENCE study continue to show that Rebif is significantly more effective in reducing frequency of relapses and magnetic resonance imaging, or MRI, activity as compared to Avonex. Final 63-week data from the EVIDENCE study showed that 56% of patients who received Rebif did not have a relapse during this observation period compared to 48% of Avonex patients. Rebif patients had a 17% relative increase in remaining free of relapses over the 63 weeks compared to Avonex patients. These data further support the benefit of increased dose and frequency of interferon administration in the treatment of relapsing forms of MS. The findings are consistent with data comparing Rebif and Avonex at 24 and 48 weeks.

At the conclusion of the comparative phase of the EVIDENCE study, patients randomized to Avonex were offered our MS therapy, Rebif. Approximately 73% of Avonex patients (n=223) chose to convert to Rebif. In June 2003, we reported that patients who converted from Avonex to higher dose, higher frequency Rebif showed a significant reduction in frequency of relapses and MRI lesion activity. Following their change in therapy, these patients experienced a 50% relative reduction in the frequency of relapses ($p<0.001$) and a 22% relative reduction in MRI lesion activity ($p=0.022$) compared to the previous six months.

In September 2003, we presented new data from a long-term assessment of a group of patients with RRMS on Rebif therapy. The eight-year extension data come from an open-label follow-up of the PRISMS study, a double-blind, placebo-controlled study that began in 1994 and involved 560 patients at 22 centers in nine countries. Patients were originally randomized to receive Rebif 44 mcg subcutaneously three times per week, Rebif 22 mcg subcutaneously three times per week or placebo. 381 patients (67% of the original cohort) were followed up after eight years. The results support the long-term benefit of Rebif 44 mcg subcutaneously three times weekly in the treatment of RRMS on relapses, disability and MRI outcomes measured, with a favorable risk benefit profile through eight years.

In October 2004, we presented data from a prospective pre-planned crossover analysis of the PRISMS study showing that patients with RRMS who were treated for two years with placebo and then treated for two years with Rebif showed substantial clinical benefits with a 54% relative reduction in relapse rate. The data also showed a significant improvement in MRI results for patients treated with Rebif 44 mcg. There was a highly, statistically significant relative reduction in the mean number of brain lesions of 67%. In addition, 76% of patients treated with Rebif 44 mcg remained free of disease progression during the two years of treatment.

In January 2004, we initiated a post-registration head-to-head study of Rebif versus Copaxone (glatiramer acetate) given at approved doses. The objective of the trial is to compare the safety and efficacy of Rebif and glatiramer acetate in RRMS patients to obtain data that will support an evidence-based approach to rational treatment decisions in MS. The study design is a two-year study with a relapse-related primary endpoint as well as other clinical and MRI secondary endpoints. The doses of study drugs are the standard doses of Rebif (44 mcg three times per week) versus glatiramer acetate (20 mg daily) both given by subcutaneous injection. In January 2005, we announced the completion of patient enrolment into this study with over 700 patients enrolled.

In May 2004, we announced the launch of the Rebiject II auto-injector, a device specifically designed to make self-injection of Rebif more convenient for MS patients on Rebif therapy, in Europe and we launched Rebiject II in the United States at the end of 2004. A study conducted in 115 patients with MS on Rebif therapy showed that 71% of those patients found the Rebiject II was better than their previous autoinjection method of injection, with patients indicating that injections using the Rebiject II were less painful and that the Rebiject II was easier to use than their previous autoinjection method of injection.

We have registered Rebif for the treatment of MS in 87 countries, including the United States, Canada, Australia, and all of the countries of the European Union.

Novantrone

In December 2002, we completed a license and commercialization agreement with Amgen, pursuant to which we acquired the rights to sell the MS and oncology drug Novantrone in the United States. Novantrone is a topoisomerase II inhibitor, which acts by inhibiting DNA replication in dividing cells. The drug is approved in the United States for secondary progressive, progressive relapsing and worsening relapsing-remitting MS and for certain forms of cancer. Novantrone has orphan drug status in the United States for use in patients with the approved MS indications until October 2007. In March 2003, we entered into an agreement with OSI Pharmaceuticals pursuant to which OSI markets and promotes Novantrone in the United States for its approved oncology indications. Novantrone is strategic for our neurology franchise in the United States as it is complementary to Rebif and allows us to leverage investments made in our neurology infrastructure. In 2004, Novantrone was our fifth largest selling product, accounting for $83.9 million or 3.9% of total product sales.

Product Pipeline

Our product pipeline in the field of neurology includes projects targeted toward improving the delivery of Rebif and discovery projects seeking new approaches to the treatment of MS.

Mylinax

In October 2002, we entered into a worldwide agreement with IVAX to develop and commercialize cladribine (now known as Mylinax), as potentially the first orally effective disease modifying treatment for MS. Mylinax is a purine-analogue that interferes with the behavior and the proliferation of certain white blood-cells, including monocytes and lymphocytes, which are involved in the pathological process of MS. Data from earlier trials suggest that injected Mylinax may be effective in certain MS patients. We have worked with IVAX to establish an oral formulation of Mylinax and initiated Phase I clinical trials in the fourth quarter of 2003. We obtained positive results from these trials in March 2004. Following discussions with regulatory authorities, we decided to initiate a Phase III clinical trial in early 2005. Cladribine is currently approved for patients with active hairy cell leukemia.

MMP-12 inhibitor

An MMP-12 inhibitor, an orally active matrix metalloprotease inhibitor with potential as a treatment for MS, entered Phase I clinical development in January 2005. Data from preclinical trials shows efficacy in an animal model of relapsing remitting MS.

JNK inhibitor

A JNK inhibitor, an orally active small molecule inhibitor of apoptosis, with potential as a treatment for MS, entered Phase I clinical development in 2004. This molecule demonstrated a promising profile in experimental models of progressive MS.

Osteopontin

Osteopontin, a naturally occurring protein with potential to remyelinate damaged neurons, entered preclinical development in 2003 and could become a treatment for multiple sclerosis as well as various demyelinating neuropathies of the peripheral nervous system.

Reproductive Health

We are the global market leader in the treatment of human infertility and have a broad offering of products in the field. The World Health Organization estimates that eight to 12 percent of all couples experience some form of infertility problem during their reproductive lives. We estimate that sales of our products currently account for more than 46% of the approximately $1.2 billion global gonadotropin market and sales of Gonal-f currently account for about 62% of the approximately $900 million global recombinant FSH segment.

In women, the maturation of ova in the ovary and subsequent maintenance of pregnancy depend on three main gonadotropins: follicle stimulating hormone, or FSH, luteinizing hormone, or LH, and human chorionic gonadotropin, or hCG. In a normal menstrual cycle, the hypothalamus produces gonadotropin releasing hormone or GnRH, which controls the release of FSH and LH. FSH stimulates estrogen production of the ovaries and the maturation and development of follicles. The mid-cycle LH surge induces ovulation, resulting in the formation of the corpus luteum, which, besides other factors, produces progesterone and estrogen. Upon conception, hCG is produced by the trophoblast, stimulating progesterone production of the corpus luteum graviditatis to maintain the pregnancy. In men, FSH stimulates spermatogenesis, and LH stimulates testosterone production of Leydig cells.

Our goal in the reproductive health area is to offer fertility products addressing the major steps in the infertility treatment process. With Gonal-f, Ovidrel and Luveris, we have implemented our strategy of replacing our urine-derived reproductive health products with recombinant versions. At the end of 2002, we decided to proceed with the closure of our production facilities for urine-derived products. We stopped selling urine-derived products in the European Union in 2003, in the United States in the second quarter of 2004, and in the rest of the world (except for Japan, where our recombinant gonadotropins are not yet approved) by the end of 2004.

Major Steps in the Infertility Treatment Process

- Ø Pituitary down-regulation—Cetrotide
- Ø Ovarian stimulation—Gonal-f, Luveris, Serophene, anastrozole (in development)
- Ø Follicular maturation and ovulation triggering—Ovidrel
- Ø Luteal phase support—Crinone
- Ø Treatment of preterm labor. Prevention of preterm delivery is one of the major challenges in perinatology. We currently have two products in pre-clinical development - an oxytocin receptor antagonist and a prostanoid FP receptor antagonist - which have potential in the treatment of preterm labor.

Recombinant Products

Sales of our recombinant products have grown in recent years and currently stand at approximately 94% of our total gonadotropin sales worldwide. We believe that use of recombinant products has increased due to the greater efficacy of recombinant products and the superior tolerance of the products by patients. These products are administered subcutaneously — just under the skin — using a small needle, which is a significant advantage over some of the urine-derived products that must be given through more painful intramuscular injection. We are continuing to encourage the switch to recombinant products, because we believe them to be superior. With Gonal-f, Ovidrel and Luveris, we are the only company that offers a totally recombinant gonadotropin portfolio.

Gonal-f

Gonal-f, the first recombinant drug developed for the treatment of infertility to receive marketing approval anywhere in the world, is a human FSH. Gonal-f is the global market leader, having been approved for use in 95 countries, including the entire European Union and the United States. It is indicated for the treatment of patients suffering from ovulation disorders. Gonal-f also stimulates the development of multiple follicles in women being treated with assisted reproductive technologies, such as in vitro fertilization, in which eggs are extracted from a woman’s body, fertilized and then inserted in the uterus. A multi-dose presentation of Gonal-f is available in the European Union, the United States and other countries and accounted for 64.7% of Gonal-f sales in 2004. Gonal-f is also approved in the European Union, the United States and other countries for treating a sub-form of male infertility called

hypogonadotropic hypogonadism. In 2004, Gonal-f was our second largest selling product, accounting for $572.7 million (26.3%) of total product sales.

Several randomized studies designed to compare Gonal-f to the urine-derived gonadotropins we formerly manufactured have shown that Gonal-f is more effective in increasing the number of follicles and embryos obtained during treatment with assisted reproductive technologies. Based on the latter studies, the European Commission permitted the labeling of Gonal-f to be amended to include a statement that it is more effective than urine-derived FSH preparations.

In order to control product variability, we have developed a highly controlled manufacturing process for Gonal-f. This manufacturing process allows us to produce recombinant human FSH with a highly consistent isoform profile and highly consistent batch-to-batch bioactivity, which is measured by a precise physico-chemical method to determine the potency of the product. As a result, Gonal-f is now filled-by-mass (i.e., protein weight). By doing so, we eliminate the intrinsic variability of the rat bioassay and ensure high batch-to-batch and vial-to-vial consistency of r-hFSH content. In 2004, we received European Union and U.S. FDA approval for our pre-filled liquid pen injector, which is designed to improve the patient-friendliness of Gonal-f injections.

Ovidrel/Ovitrelle

Our recombinant hCG, which we market as Ovidrel in the United States and Ovitrelle in the European Union, is used to induce final maturation of ovarian follicles and to trigger ovulation. hCG is a hormone produced by the human placenta that acts in a similar manner to LH. A monthly surge in the production of LH is responsible for ovulation. The hCG contained in Ovidrel triggers ovulation in a way similar to the way LH does in a natural monthly menstrual cycle. Ovidrel is registered in 70 countries. Recombinant hCG is better tolerated by patients and can be administered through subcutaneous injection, a significant patient advantage over earlier urine-derived products, which had to be given by intramuscular injection. In October 2003, the Ovidrel/Ovitrelle pre-filled syringe was approved by both the FDA and the European Commission, making it the first liquid, ready-to-use recombinant hCG. In 2004, Ovidrel accounted for $17.7 million or 0.8% of total product sales. As of November 2004, in the United States Ovidrel was the number one product in the hCG market segment, which includes many generic competitors.

Luveris

Luveris is the first product ever developed in which LH is available as a stand-alone hormone. Luveris provides a pure source of recombinant LH for the small population of patients that have a deficiency of both LH and FSH (LH <1.2 IU/L) and therefore require treatment with both hormones to achieve pregnancy. We have marketed Luveris in the European Union since mid-2001. In October 2004, the U.S. FDA approved Luveris for concomitant use with Gonal-f for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency. We launched Luveris in the United States in the last quarter of 2004. The U.S. FDA has granted Luveris orphan drug status until October 8, 2011. Luveris is registered in 67 countries.

Urine-Derived Products

At the end of 2002, we decided to proceed with the closure of our production facilities for urine-derived products. We stopped selling urine-derived products in the European Union in 2003, in the United States in the second quarter of 2004, and in the rest of the world (except for Japan where our recombinant gonadotropins are not yet approved) by the end of 2004. As a result of our decision to phase out these products, sales of our urine-derived gonadotropins were $38.2 million, down by 57.2%, in 2004.

Pergonal

Pergonal is a preparation of FSH and LH for intramuscular injection extracted from the urine of post-menopausal women. It is indicated for use in inducing ovarian follicular growth in infertile women with ovulation disorders. In addition, it may be used to stimulate the development of multiple follicles in patients having treatment with assisted reproductive technologies. Pergonal, when administered to men at the same time as hCG, is indicated for the stimulation of sperm formation in patients who have a form of male infertility.

Metrodin HP

Metrodin HP, which was marketed in the United States as Fertinex, is a highly purified preparation of FSH extracted from the urine of post-menopausal women. Metrodin HP contains 95% FSH, a much higher percentage than first generation gonadotropin preparations. Metrodin HP was used for many of the same indications as Gonal-f, which has largely replaced Metrodin HP. In 2004, Metrodin HP accounted for $15.9 million or 0.7% of total product sales.

Profasi

Profasi consists of hCG derived from the urine of pregnant women. Profasi is given to women to induce final follicular maturation and trigger ovulation, once follicular development has been achieved by treatment with products such as Gonal-f, Metrodin HP or Pergonal. Profasi is administered to men with certain types of infertility to enhance the production of testosterone, a hormone essential in the development of sperm. It is also indicated for the support of luteal function in women with certain fertility disorders. Profasi is used for many of the same indications as Ovidrel, which has replaced Profasi.

Other Products

Crinone

Crinone is a progesterone product with an advanced delivery technology that permits it to be self-administered as a vaginal gel. Progesterone is a hormone that is required to prepare the lining of the uterus for the implantation of a fertilized egg and for the maintenance of pregnancy. The gel is used in connection with certain assisted reproductive technologies, including in vitro fertilization. Crinone is associated with high clinical pregnancy rates and is convenient for patients, because it is user friendly and does not require painful intramuscular injections. It is the only progesterone product with marketing authorization for infertility treatment in Germany and the United Kingdom. In July 1999, we acquired exclusive worldwide marketing rights to Crinone, which we license from Columbia Laboratories. Pursuant to this license, Columbia Laboratories supplies Crinone to us for resale. The agreement will be in effect for four more years, after which it is renewable for additional five-year terms. In April 2001, we withdrew Crinone from the market due to a manufacturing defect. In March 2002, we relaunched Crinone in the United States and reintroduced Crinone in other worldwide markets later in 2002. As a part of our settlement of litigation with Columbia Laboratories related to the recall, we amended our marketing agreement for Crinone. Under the amended agreement, we will continue to market Crinone outside the United States and to reproductive endocrinologists, obstetricians and gynecologists who prescribe injectable gonadotropins in the United States, and Columbia Laboratories will market a second brand of its product to other obstetricians and gynecologists in the United States in exchange for royalty payments to us. In 2004, Crinone accounted for $19.8 million or 0.9% of total product sales. Crinone is registered in 50 countries.

Cetrotide

In ovarian stimulation for assisted reproductive techniques such as IVF (in vitro fertilization) or ICSI (intracytoplasmic sperm injection), the successful prevention of a premature LH surge is crucial. Cetrotide is the first LHRH antagonist in the world to be approved for the prevention of the LH surge. Treatment with Cetrotide is generally more convenient than treatment with LHRH agonists, which involves prolonged therapy to achieve pituitary down-regulation. We market Cetrotide under an agreement with Zentaris (formerly Asta Medica) which gives us the right to market, distribute and sell Cetrotide worldwide, with the exception of Japan. The agreement expires in 2020. Thereafter, we have a perpetual fully paid up license. We currently market Cetrotide in 79 countries. In 2004, sales of Cetrotide accounted for $24.8 million or 1.1% of total product sales. We provide Cetrotide in two different doses: 0.25 mg for multiple dose application and 3 mg for single dose application. It has been shown and published in peer-reviewed journals that the tolerability of Cetrotide is better when compared to a similar product provided by a competitor. Furthermore, the application of the single-dose Cetrotide protocol results in significantly fewer injections for the patient compared with the competitor’s product.

Product Pipeline

Gonal-f

We are currently consolidating our worldwide labeling for Gonal-f by seeking to register it in additional jurisdictions or for additional indications in jurisdictions where we already have approval. For example, in 2004 we filed for Gonal-f in Japan and the application is currently under review by the Japanese health authorities.

Onercept

Onercept, or TBP-1, is a recombinant, soluble type I TNF receptor which acts as an inhibitor of tumor necrosis factor (TNF) alpha. Based on preclinical data suggesting that blocking TNF inhibits the development of endometriotic lesions, we plan to start a proof of concept trial in endometriosis in 2005.

Anastrozole

In July 2002, we entered into an exclusive worldwide agreement with AstraZeneca pursuant to which we have the right to develop, register and market the aromatase inhibitor anastrozole in ovulation induction and improvement of follicular development. Anastrozole is an oral aromatase inhibitor, which acts by blocking the synthesis of estrogen and thereby improving ovulation. Because of its characteristics, we hope it will have benefits over currently available treatments, both in terms of efficacy and having fewer side effects. We commenced a Phase II trial of the drug investigating single doses in this indication in the first quarter of 2003, which showed that monofollicular development with ovulation and pregnancy can be achieved in the target population. Results indicate that the dose regimen could be further optimized before entering Phase III. Therefore, we plan to start a further Phase II multiple-dose dose-finding, comparative trial versus clomiphene citrate in the first half of 2005. Anastrozole is currently sold by AstraZeneca under the trade name Arimidex for the treatment of breast cancer in approximately 100 countries worldwide.

Oxytocin Receptor Antagonist

We are developing a low molecular weight oxytocin receptor antagonist which can be administered orally and has potential as a treatment for premature labor. Results from a Phase I clinical trial with a lead molecule indicated that this was not optimal. A new optimized lead has been identified and preclinical studies are ongoing.

Prostanoid FP Receptor Antagonist

We are developing a low molecular weight prostanoid FP receptor antagonist which can be administered orally and has potential as a treatment for premature labor. This compound is currently in preclinical development.

Growth and Metabolism

Human growth hormone is used in the treatment of growth retardation in children and the treatment of AIDS Wasting, growth hormone deficiency and short bowel syndrome in adults. We estimate that the worldwide human growth hormone market generated approximately $2.1 billion in sales in 2004, based on publicly reported sales data for Saizen, Serostim and Zorbtive and five competing products.

Growth

Children may experience growth retardation as a result of a variety of conditions. These include growth hormone deficiency, Turner’s syndrome, a genetic disease that affects girls, and chronic renal failure. Growth hormone deficiency is associated with abnormally low levels of pituitary growth hormone.

Saizen

Saizen is recombinant human growth hormone. We introduced Saizen in 1989, and it is now

- Approved in 81 countries, including the U.S., for the treatment of growth hormone deficiency in children;

- Approved in 18 E.U. countries, the U.S. and 25 other countries for treatment of growth hormone deficiency in adults;

- Approved in 72 countries, excluding the U.S., for the treatment of growth failure due to Turner's syndrome; and

- Approved in 38 countries, excluding the U.S., for treatment of children with growth failure associated with chronic renal failure.

In May 2004, we filed an application in Europe for use of Saizen in children who were born too small for gestational age. This indication sometimes is known as intra-uterine growth retardation. In 2004, Saizen was our third largest selling product, accounting for $182.1 million or 8.4% of total product sales.

Saizen is available worldwide in freeze-dried formulations containing 8.8 mg and 5 mg that is stable at room temperature before reconstitution, and is therefore more easily stored and more convenient for patients than some competing drugs. Because growth retardation primarily affects children and requires long-term treatment with daily injections, delivery systems are a key differentiator among competing products. Saizen is delivered by two innovative delivery devices: one.click (autoinjector) and cool.click (needle-free). One.click enables the needle to be introduced automatically under the skin, significantly reducing the pain of injection. We launched one.click in Europe in 2001 and in the United States in September 2004. Cool.click is a needle-free delivery system and was the first needle-free device to be launched in the United States for use with human growth hormone. We launched cool.click in the United States in September 2000 and in Europe in the third quarter of 2002, and we are currently rolling it out worldwide.

In October 2000, we expanded our agreement with Bioject to give us the right to use Bioject's Vitajet 3 needle-free injection system, which is the basis for cool.click, in all current and future human growth hormone products and indications worldwide. In addition, we obtained exclusive options to use all new technologies developed by Bioject for the delivery of human growth hormone.

Metabolism

AIDS Wasting. AIDS Wasting is associated with decreased survival in AIDS patients. It is caused by a disturbance in the patient's metabolism that interferes with the body's effective use of nutrients. This metabolic disturbance causes the body to break down vital organ and muscle tissue, known as lean body mass, to generate energy while at the same time conserving fat. AIDS Wasting is a metabolic condition that is independent of the level of the HIV virus. Clinical data have shown that without critical lean body mass, HIV patients get sick more often and may not live as long as those who are not losing lean body mass.

Conventional treatments for AIDS Wasting, such as appetite stimulants, generally do not help patients regain lean body mass, because they do not treat the underlying metabolic cause of AIDS Wasting. Though protease inhibitors, which are used in the treatment of AIDS, can cause patients to gain weight, studies show that a significant percentage of patients on optimal protease inhibitor therapy still suffer from wasting.

Serostim

Serostim is our recombinant human growth hormone formulation which is approved for the treatment of AIDS Wasting in the U.S., Japan and 11 other countries. In 2004, Serostim was our fourth largest selling product, accounting for $86.8 million or 4.0% of total product sales.

Serostim reverses the underlying metabolic disturbance that occurs in AIDS Wasting through its protein building and protein sparing activity, which promotes a significant increase in patient lean body mass and weight. It remains the only growth hormone whose safety and efficacy for treating AIDS Wasting has been proven in a double-blind, placebo-controlled setting.

Serostim is also the first and only human growth hormone approved for AIDS Wasting by the FDA. In August 2003, following completion of a 750-patient, multi-center, placebo-controlled study which confirmed that Serostim improved physical performance, and increased lean body mass and decreased truncal fat, the U.S. FDA granted Serostim full approval for treatment of AIDS Wasting, confirming the accelerated approval that had been granted in 1996. During 2001, we received FDA clearance for a needle-free device, SeroJet, to deliver Serostim. SeroJet was developed in partnership with Bioject under the exclusive licensing agreement we entered into in October 2000. We launched SeroJet in the United States in February 2002.

Short Bowel Syndrome. Short bowel syndrome, or SBS, is a rare, serious and potentially life-threatening condition that follows extensive surgical removal of portions of the small intestine as a result of disease or trauma. Removal of a

large portion of the bowel results in impaired absorption of nutrients. Currently the standard treatment for SBS involves careful management of dietary intake and hydration or, where appropriate, a process referred to as parenteral nutrition in which patients are fed through an intravenous tube. On rare occasions, surgical transplant of the intestine may also be performed for this condition. There are an estimated 10,000-20,000 patients in the United States who are receiving intravenous parenteral nutrition for SBS.

Zorbtive

Zorbtive is our trade name for our recombinant human growth hormone indicated for short bowel syndrome. In a randomized, double-blind, controlled, parallel group Phase III clinical study, Zorbtive administered with specialized nutritional support was shown to significantly reduce patient dependence on total parenteral nutrition as measured by total volume and frequency of infusion. In December 2003, the U.S. FDA approved Zorbtive for use in the treatment of SBS. We launched Zorbtive in the United States in May 2004. The FDA has granted Zorbtive orphan drug exclusivity for use in the treatment of patients with SBS until December 2010.

Product Pipeline

Serostim in HARS

HIV-Associated Adipose Redistribution Syndrome, or HARS, is an abnormal accumulation of truncal adipose tissue (including visceral fat) in people infected with HIV. It is a rare condition and is a subset of abnormal disorders of fat distribution and altered metabolism often called HIV-related lipodystrophy. In March 2004, the FDA granted orphan drug designation for the use of human growth hormone in this indication in the United States. In the second quarter of 2004, we initiated a Phase III clinical trial of Serostim for the treatment of HARS. The trial was fully enrolled by the end of 2004.

PTB1b inhibitor

A protein tyrosine phosphatase 1b inhibitor with potential as a treatment for diabetes and obesity entered Phase I in the fourth quarter of 2004.

Dermatology

In addition to strengthening our existing core therapeutic areas, our strategy is to expand our product offerings into new highly specialized markets where there are major unmet medical needs. As part of that strategy, in August 2002, we entered into an agreement with Genentech to market the psoriasis drug Raptiva (efalizumab). Under our agreement, we have the exclusive license to market Raptiva worldwide, except in the United States and Japan. We will also collaborate with Genentech and its U.S. partner Xoma on co-developing other indications for Raptiva. As of January 2005, Xoma is no longer involved in the development of Raptiva but receives royalties from Genentech.

Psoriasis is a chronic autoimmune disease with an average prevalence of about 2% in Europe and the United States. Approximately one quarter of these patients have moderate or severe forms of the disease. The disease is characterized by the abnormal growth of new skin cells, resulting in thick, red, scaly, inflamed patches. Psoriasis can be limited to a few spots or involve extensive areas of the body. There is no known cure for the disease. While some current treatments for psoriasis may help control the symptoms of the disease, their benefits are not long-lasting and they may be associated with serious side-effects. It is estimated that the currently available therapies are ineffective or inappropriate in about 20% of moderate-to-severe psoriasis patients.

Product

Raptiva

Raptiva (efalizumab) is a humanized monoclonal antibody designed to inhibit three key inflammatory processes in the series of events that are associated with psoriasis. It is administered subcutaneously once per week. In July 2004, we announced preliminary 30-month results from an open-label study evaluating the safety and efficacy of long-term continuous treatment with Raptiva in adults with moderate-to-severe chronic plaque psoriasis. The results of the study

suggest that continuous, weekly dosing of Raptiva provided sustained clinical benefit over 2.5 years. Of the 159 subjects participating in the study who completed 30 months of treatment, a 75% or greater improvement on the Psoriasis Area Sensitivity Index, or PASI, was observed in 75% of patients with weekly Raptiva therapy (as-treated analysis). Ninety-one percent of patients achieved an improvement of 50% on the PASI and 45% of patients achieved a 90% or greater improvement on the PASI (as-treated analysis).

In September 2004, we received authorization to market Raptiva in the 25 countries of the European Union for people with moderate-to-severe chronic plaque psoriasis for whom other systemic treatments or phototherapy have been inadequate or inappropriate. Raptiva is the first biologic treatment for psoriasis to be authorized for marketing in the European Union. Raptiva is registered in the E.U., U.S. and 12 other countries (Argentina, Australia, Brazil, Bulgaria, Hong Kong, Iceland, Korea, Mexico, Norway, Romania, Singapore and Switzerland). We have made Raptiva available in Germany, Austria, Greece, Ireland, Hong Kong, Portugal, Norway, UK, Denmark, Sweden, Switzerland, Australia, Argentina, Mexico and Singapore**.** We expect that the roll-out of Raptiva will continue throughout 2005 with the launch in major European markets such as France, Spain and Italy and in Canada.

Product Pipeline

Onercept

Onercept, or TBP-1, is a recombinant, soluble type I TNF receptor which acts as an inhibitor of tumor necrosis factor (TNF) alpha, a cytokine that can cause irreversible damage to organs when secreted in excessive amounts by people with inflammatory and other diseases. Following the announcement of positive Phase II results for onercept in psoriasis in 2003, we initiated a multicenter, multinational Phase III program in the third quarter of 2004. Onercept has already been shown to have a highly competitive efficacy profile in Phase II, with more than 50% of patients achieving a 75% improvement in PASI score after 12 weeks.

Research and Development

Research and development is vital to our ability to continue to grow our business. We employ 1,387 research and development personnel, and our R&D expenses were 24.2% of our total revenues in 2004. R&D efforts are spearheaded by our scientists at the Serono Pharmaceutical Research Institute in Geneva, Serono Reproductive Biology Institute in Boston, Serono Genetics Institute (formerly Genset S.A.) in Evry, France and Istituto di Ricerca Cesare Serono and Istituto di Ricerche Biomediche ‘‘Antoine Marxer’’ RBM in Italy, with important contributions provided under collaborative arrangements with other biotechnology companies and institutions, particularly the Weizmann Institute of Science in Israel. Our discovery group at the Serono Pharmaceutical Research Institute focuses on drug discovery in neurological diseases like MS, autoimmune diseases and wasting. The Serono Reproductive Biology Institute concentrates on reproductive health and related clinical indications. Serono Genetics Institute focuses on genomics research. During 2002, 2003 and 2004, we spent $358.1 million, $467.8 million and $594.8 million, respectively, on research and development.

As a leader in the field, we are committed to taking full advantage of the opportunities presented by biotechnology. We have concentrated on establishing state-of-the-art skills in those technologies that will significantly enhance our ability to deliver innovative products to specialist markets. Our R&D efforts are focused on:

- Ÿ pursuing drug discovery efforts that may lead to new products;
- Ÿ enhancing our discovery capabilities through research partnerships;
- Ÿ improving drug delivery of our protein therapeutics;
- Ÿ strengthening our key therapeutic areas through new products and line extensions; and
- Ÿ developing products in new therapeutic areas, such as oncology.

Pursuing Drug Discovery

We are actively seeking new therapies for new indications. Our molecular biologists are using DNA sequencing and identification technologies to identify new drug targets in the human genome. We can monitor the genes expressed in a cell at a particular time by integrating data from gene chips and gene filters. Working with clinical groups around the world, we are able to use our data to identify how genes are expressed in connection with different diseases. By understanding how genes are expressed in connection with different diseases, we identify points of intervention at which molecules may alter the progression and development of the diseases. We then determine whether the point of intervention would be best addressed through the use of protein therapeutics or therapies using smaller molecules.

Advances in chemistry, screening technology and robotics allow us to rapidly test a multitude of compounds to see if any one of the compounds may be used to treat a given disease process. We use high throughput screening and combinatorial chemistry techniques to try to identify small molecules that may have beneficial therapeutic effects on targeted disease processes.

High throughput screening is a technique for quickly screening many possible treatments for a specified condition. The process starts by selecting a type of cell that will react in accordance with a specified disease process. To do this we often genetically modify cells to give them the characteristics we desire. We then select a large number of small, simple molecules that we believe may have a positive therapeutic effect on the disease process. The cells are then exposed to the different molecules, and we select those that, based on their effect on the cells, appear to hold the greatest promise as future therapies. Once we have narrowed the field of potential molecules, using combinatorial chemistry techniques we modify them in different ways to determine whether a slightly different structure of the same basic molecule may have a more powerful effect on the disease process. We then assess whether the molecules we have identified are appropriate for preclinical trials.

In September 2002, we significantly increased our drug discovery capability through our acquisition of Genset S.A. Genset, now the Serono Genetics Institute, provides us with leading expertise in the linkages between genes and diseases, a strong scientific team, an extensive cDNA library of secreted proteins and an integrated technology platform in bioinformatics, genetics, biostatistics and therapeutic genomics.

Our research has helped us to identify several potential new therapeutic compounds that are currently in preclinical development.

Neurology

- Osteopontin, a molecule with potential to remyelinate damaged neurons, entered preclinical development in 2003 and could become a treatment for various neuropathies, including MS.

Reproductive Health

- An orally available low molecular weight prostanoid FP receptor antagonist with potential as a treatment for premature labor entered preclinical development in 2003.

- A new lead molecule of an orally available low molecular weight oxytocin receptor antagonist with potential as a treatment for premature labor entered preclinical development in 2004.

Autoimmune/inflammatory diseases

- The antisense compound Kappaproct is undergoing additional preclinical trials to establish a more solid proof of principle in its use in inflammatory diseases as well as a more adequate dosing regime for ulcerative colitis patients.

- The cytokine tadekinig alpha is undergoing additional preclinical trials to establish whether it has potential in the treatment of autoimmune conditions.

Entering into Strategic Research Collaborations

We are also enhancing our discovery capabilities by entering into strategic research collaborations with several leading companies in the field of small molecule drug discovery.

In February 2004, we extended the collaborative research agreement signed in 2001 with Inpharmatica Ltd. Under the expanded agreement, Inpharmatica received an up-front fee for granting us additional rights to novel protein sequences delivered under the collaboration. The up-front fee has been expensed as research and development expense.

In October 2004, we entered into an agreement with Paratek Pharmaceuticals Inc. to discover, develop and commercialize an orally available disease modifying treatment for multiple sclerosis (MS). Under the terms of the agreement, Paratek received an up-front fee and a loan convertible into Paratek stock and will receive research funding and milestone payments related to development progress and regulatory milestones. In addition to the up-front consideration, Paratek would receive $38.0 million in milestone payments for the first product to be successfully developed and registered in MS. The initial fees have been expensed as research and development expense.

In October 2004, we entered into a broad alliance with ZymoGenetics Inc. to research, develop and commercialize novel protein and antibody therapeutics based on discoveries made by ZymoGenetics. As part of this alliance, we will gain access to a portfolio of ZymoGenetics' genes and proteins, will have rights over the next five years to license up to 12 products, and will have exclusive worldwide rights to develop and commercialize products based on Fibroblast Growth Factor 18 (FGF-18) and the Interleukin 22 Receptor (IL-22R). In addition, the companies will co-develop Interleukin 31 (IL-31). Under the terms of the agreement, we paid ZymoGenetics an up-front fee of $20.0 million in exchange for the rights to license proteins over the next five years, paid $11.3 million for entering into three license agreements and purchased $50.0 million of ZymoGenetics' common stock. We will pay a series of milestone payments, will share all profits from the co-commercialization of products in the United States for which ZymoGenetics has co-funded development, and will pay royalties on eventual sales of the products outside the United States and, to the extent ZymoGenetics elects not to co-develop products, on product sales in the United States. The up-front fee and license fees have been expensed as research and development expense. The purchase of common stock was recorded as an available-for-sale equity investment.

In November 2004, we signed a worldwide agreement with Nautilus Biotech to develop the next-generation of human growth hormone, with improved biological, pharmacological and clinical profiles. Under the terms of the agreement, Nautilus received an up-front fee and will receive potential milestone payments and undisclosed royalties on sales of the improved protein. The up-front fee has been expensed as research and development expense.

In December 2004, we entered into an agreement with Micromet AG to develop and commercialize Micromet's MT201 (adecatumumab), a pan-carcinoma monoclonal antibody directed against the epithelial cell adhesion molecule Ep-CAM for the treatment of cancers of epithelia cell origin. Under the terms of the agreement, Micromet received an initial license fee of $10.0 million and will receive additional milestone payments of up to $138.0 million if the product is successfully developed and registered worldwide in three or more indications. In addition, Micromet will receive undisclosed royalties based on net sales of the product. The up-front fee has been expensed as research and development expense.

In December 2004, we entered into a worldwide collaboration with CancerVax Corporation for the development and commercialization of Canvaxin, an investigational specific active immunotherapy product being developed for the treatment of advanced-stage melanoma. Under the terms of the agreement, we paid CancerVax an up-front fee of $25.0 million and purchased one million shares of CancerVax common stock for $12.0 million. In addition, CancerVax could receive up to $253.0 million in milestone payments for the achievement of development, regulatory and commercial milestones. The fee has been expensed as research and development expense. The purchase of common stock was recorded as an available-for-sale equity investment.

Improving Drug Delivery

An integral part of our research and development programs is the development of more patient-friendly drug delivery systems. Because most of our products must be injected under the skin, we believe easier and less painful drug delivery systems will promote patient compliance and product loyalty.

The value of protein therapeutics can be greatly enhanced by improved delivery systems. These systems may be able to provide alternatives to injection or reduce the frequency of injections. Because many of our products, such as Rebif, Gonal-f, Saizen and Serostim, must be administered frequently and Saizen is used mostly for children, we believe that many of our potential customers would consider the ease of administration to be an important factor when selecting between our products and those of our competitors. As a result, we have set up our own drug delivery laboratory and have established major collaborations with specialist drug delivery companies on projects designed to improve the delivery of all of our major protein and peptide products.

Strengthening Key Therapeutic Areas

Novel protein therapeutics were the first benefits provided by biotechnology, beginning with the replacement of naturally derived hormones and cytokines with biotechnology-derived proteins. With our production of recombinant fertility hormones, growth hormones and interferon beta, we are at the forefront of these developments.

For information on our R&D projects in the four key therapeutic areas on which we currently focus, consult the respective Product Pipeline sections for each therapeutic area (Neurology, Reproductive Health, Growth and Metabolism, and Dermatology) above.

Developing Products in New Therapeutic Areas

In addition to our continuing commitment to our existing therapeutic areas, we are also performing research and developing potential products in new areas like autoimmune diseases, gastroenterology, and oncology. Several molecules are currently in development in new therapeutic areas:

TACI-Ig. A TACI (transmembrane activator and CAML-interactor) fusion protein, which interacts with B lymphocytes and represents a novel therapeutic approach to treating autoimmune diseases, such as systemic lupus erythematosus or SLE and rheumatoid arthritis, as well as B-cell malignancies, is being co-developed with ZymoGenetics. Following the successful completion of a Phase I trial in human volunteers with this molecule, during 2004 we initiated Phase Ib clinical trials in SLE, rheumatoid arthritis and multiple myeloma, as well as a Phase I trial in relapsed or refractory B-cell malignancies.

Canvaxin. We recently acquired the worldwide rights to develop and commercialize CancerVax's specific active immunotherapy product Canvaxin for the treatment of advanced-stage melanoma, a deadly form of skin cancer. Canvaxin is currently being evaluated in two international, multi-center Phase III clinical trials for the treatment of Stage III and Stage IV melanoma.

Adecatumumab. We recently acquired the worldwide rights to develop and commercialize Micromet's antibody product adecatumumab which has potential in the treatment of a broad range of cancers of epithelial origin, including prostate, breast, colon, lung, stomach, pancreatic, head and neck, and ovarian cancer. Adecatumumab, a fully human antibody directed against the epithelial cell adhesion molecule, is currently being evaluated in two Phase II trials for the treatment of metastatic breast cancer and prostate cancer.

Kappaproct. We have acquired the worldwide rights to develop and commercialize InDex Pharmaceuticals' antisense compound Kappaproct for the treatment of ulcerative colitis. A Phase II clinical trial did not reach its primary endpoint in terms of clinical remission versus placebo; however there was a dose-response trend. Patients on the two highest dose levels went into clinical remission faster than those treated with the two lowest dose levels or the patients treated with placebo. Overall, the safety profile was good. Serono and InDex are focusing on finding a more solid preclinical proof of principle in the use of Kappaproct in inflammatory diseases and a more adequate dosing regime for ulcerative colitis patients.

Interferon beta. We are currently conducting a Phase III trial of interferon beta-1a for the treatment of Asian patients suffering from chronic hepatitis C. Results from a study completed in 2001 suggested that patients of Asian origin with this disease may benefit from r-IFN-beta.

Tadekinig alpha. In 2004, we completed Phase IIa trials of tadekinig alpha, our recombinant interleukin-18 binding protein, in psoriasis and rheumatoid arthritis. Results did not show the expected promise based on preclinical data in animal models. Preclinical investigations are ongoing to identify if tadekinig alpha has potential in the treatment of autoimmune conditions.

Major Products and High Priority R & D Projects

Product Type	Trade Name	Indications	Status as of January 31, 2005
Recombinant human interferon1a (r-IFN-ß1a)	Rebif	Multiple sclerosis	Approved in E.U. (25 countries), U.S. and 61 other countries
	*	Chronic hepatitis C in Asian patients	Phase III clinical trial
Mitoxantrone	Novantrone	Multiple sclerosis, certain cancers	Rights to commercialize approved product in U.S.; Orphan Drug Status in U.S. for MS
Cladribine	Mylinax	Multiple sclerosis	Phase III clinical trial
JNK inhibitor	*	Multiple sclerosis	Phase I clinical trial
MMP-12 inhibitor	*	Multiple sclerosis	Phase I clinical trial
Osteopontin	*	Remyelination	Preclinical
Recombinant human follicle stimulating hormone (r-hFSH)	Gonal-f	Female infertility	Approved in E.U. (25 countries), U.S. and 69 other countries
	Gonal-f	Male infertility - hypogonadotropic hypogonadisma	Approved in E.U. (25 countries), U.S. and 38 other countries
	Gonal-f	Multi-dose formulation	Approved in E.U. (25 countries), U.S. and 40 other countries
	Gonal-f	Fill by mass formulation	Approved in E.U. (25 countries), U.S. and 41 other countries
	Gonal-f	Pre-filled pen injector	Approved in E.U. (25 countries), U.S. and 10 other countries
Recombinant human luteinizing hormone (r-hLH)	Luveris	Severe FSH and LH deficiency	Approved in E.U. (25 countries), U.S. and 41 other countries; received Orphan Drug Status in U.S.
Recombinant human chorionic gonadotropin (r-hCG)	Ovidrel/Ovitrelle	Female infertility/ovulation induction and use in assisted reproductive	Approved in E.U. (25 countries), U.S. and 44 other countries

		technology	
Cetrorelix (GnRH antagonist)	Cetrotide	Premature ovulation prevention	Approved in E.U. (25 countries), U.S. and 53 other countries.
Progesterone gel (8%)	Crinone	Luteal phase support	Approved in U.S., 15 E.U. countries and 34 other countries
Anastrozole (aromatase inhibitor)	*	Ovulation induction and improvement of follicular development	Phase II clinical trial
Onercept	*	Endometriosis	Phase I clinical trial
Oxytocin receptor antagonist	*	Pre-term labor	Preclinical
Prostanoid FP receptor antagonist	*	Pre-term labor	Preclinical
Recombinant human growth hormone (r-hGH)	Saizen	Growth hormone deficiency	Approved in 81 countries
	Saizen	Growth hormone deficiency in adults	Approved in 18 E.U. countries, U.S. and 25 other countries
	Saizen	Growth failure due to Turner's syndrome	Approved in 72 countries
	Saizen	Growth failure associated with chronic renal failure	Approved in 38 countries
	Saizen	Small for gestational age babies (IUGR)	Filed in E.U.
Recombinant human growth hormone (r-hGH) high dose	Serostim	AIDS Wasting (cachexia)	Approved in U.S., Japan and 11 other countries
	Serostim	HARS/Lipodystrophy	Phase III clinical trial; received Orphan Drug Designation in U.S.
	Zorbtive	Short bowel syndrome	Approved in U.S.; received Orphan Drug Designation in U.S.
PTP1b inhibitor	*	Diabetes and obesity	Phase I
Efalizumab	Raptiva	Psoriasis	Registered in E.U., U.S. and 12 other countries

Onercept (r-TBP-1)	*	Psoriasis	Phase III clinical trial
Tadekinig alpha (r-IL-18bp)	*	Autoimmune diseases	Preclinical
TACI-Ig	*	Systemic lupus erythematosus	Phase Ib clinical trial
	*	Rheumatoid arthritis	Phase Ib clinical trial
	*	Multiple myeloma	Phase Ib clinical trial
	*	Relapsed or refractory B-cell malignancies	Phase I clinical trial
p65 inhibitor	Kappaproct	Inflammatory diseases	Preclinical
Adecatumumab	*	Prostate cancer	Phase II clinical trial
	*	Metastatic breast cancer	Phase II clinical trial
	CanVaxin	Stage IV melanoma	Phase III clinical trial

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* Trade name not yet determined

Sales and Marketing

We have marketing, sales and distribution organizations based in Europe and the United States, and we employ a sales and marketing force of 2,084 people worldwide. Because we focus on highly specialized markets with a limited number of prescribing physicians, we believe that our sales force can efficiently penetrate each of our target markets. In general, our products are sold to wholesale distributors or directly to pharmacies or medical centers. We utilize common pharmaceutical company marketing techniques, including physician detailing, advertising, targeting opinion leaders and other methods. We also employ marketing strategies specific to our individual product lines.

Neurology

In certain markets we focus on neurologists that specialize in MS. In other markets we focus on general neurologists.

In the United States, we promote Rebif directly through our own sales force and, in addition, since October 2002, through a second sales force operated by Pfizer Inc. under a copromotion agreement under which we have agreed to share U.S. marketing and development costs. Pfizer has an established neurology franchise.

Our agreement with Pfizer allows us to contact a much larger proportion of the expanding prescriber base more frequently than we would have been able to contact acting alone. We believe that Pfizer's presence in the neurology therapeutic area helps us more quickly and effectively distribute the message of Rebif's attributes.

Outside the United States, we are committed to continuing medical education programs, which examine the latest developments in MS, including research and treatments. Our programs in the United States focus on the scope of treatment protocols to address all aspects of the disease and helping medical professionals learn more about ways to offer the highest level of patient care. A major initiative in 2004 was the establishment of the MSBase Foundation to run the state-of-the-art MS registry independently of Serono for the benefit of physicians and their patients.

In 2003, we introduced new resources for the MS community in the United States, including the Learning for life empowerment series as well as the newly enhanced MSLifeLines.com website. The Learning for life series offers an array of information to people living with MS and provides a jumping off point for doctors and patients to communicate better about the specific treatment needs of each patient. Specifically, the empowerment series provides in depth information on use of MRI, parameters to consider in evaluating therapy as well as information on the disease and the different treatment options available for people with MS.

Outside the U.S. we have well-established call centers and nurse programs in many countries to provide support and guidance for MS patients generally and specifically to help with the introduction of Rebiject II and the new 29G needle. In addition to this we have provided help with access to MRI facilities to aid diagnosis in some regions. We are active in lobbying for patients to have greater access to therapy and for MS to receive a higher priority on national healthcare agendas. In particular, we provide support to the European MS Platform and to the Multiple Sclerois International Federation patients associations.

Reproductive Health

We focus our reproductive health marketing efforts on educating and informing reproductive endocrinologists about treatment options for infertility.

In February 2004, we announced the launch of www.fertility.com, a new website for patients outside the United States, which offers a definitive source of information for people who have concerns about their fertility or are seeking or undergoing treatment. This new website provides comprehensive facts and describes therapy throughout each stage of the patient journey, from any initial concerns about infertility to a potential pregnancy. The website provides people

who are concerned about their chances of having a child with information on the physiology of reproduction and causes of possible fertility disorders. For those considering therapy, it outlines the various options available to them. It also provides advice to patients already undergoing treatment. Finally, recommendations are given to couples on the lifestyle choices and medications that may help to support early pregnancy. The website contains a variety of useful links to patient associations as well as references for further reading. For the United States market, we relaunched www.seronofertility.com, which includes comprehensive infertility information for consumers and patients, as well as interactive tools such as a “find a specialist” service, which allows visitors to find local reproductive endocrinologists. The site also features animated, narrated patient instructions for mixing and injecting Serono products. To drive traffic to seronofertility.com, we implemented web advertising programs on popular consumer sites such as google.com, WebMD.com and babycenter.com.

We also have a number of ongoing initiatives that are designed to support access to infertility treatment. In the United States, we launched the first ever manufacturer-sponsored direct-to-consumer (DTC) advertising campaign in the infertility market in June 2003, including television, radio, magazine and web advertising. Consumers and patients who call our free educational service, Fertility LifeLines, toll-free at 1-866 LETS TRY receive customized educational materials via mail, including a list of local fertility centers. In several major markets, including Germany, Spain and the UK, we have performed pharmaco-economic study programs to demonstrate the cost benefit of recombinant products versus urine-derived preparations. This activity supports our strategy to help establish and maintain reimbursement for our products. For those patients in the United States who are not eligible for reimbursement, do not have appropriate insurance coverage and are unable to pay for the treatment themselves we have a Compassionate Care program. This program helps provide patients that meet certain criteria with access to our infertility products at no cost.

Growth and Metabolism

Growth

We focus our marketing of growth products on capturing new patients, since patient loyalty is particularly strong in this market. To do this we target pediatric endocrinologists and leading pediatricians in clinics and treatment centers. We implement medical clinical programs and set up innovative registries. We are also developing new drug delivery devices for use in this market, where patient convenience is particularly important. In September 2000, we launched cool.click, a needle-free delivery system for Saizen, which is the first needle-free delivery system for human growth hormone in the United States and Canada. We launched cool.click in Europe in the third quarter of 2002 and are currently rolling it out worldwide. In September 2004, we launched our autoinjector pen device for growth hormone, one.click, in the United States. The U.S. FDA also granted approval for Saizen to be promoted in the Adult Growth Hormone Deficiency market. This indication will be launched in early 2005.

Metabolism

Our sales and marketing efforts for our AIDS Wasting product focus on the education of HIV/AIDS-treating physicians and their staffs and nurses that work with the patients. In addition to focusing on the therapeutic benefits of Serostim, our sales and marketing efforts are directed toward education about AIDS Wasting.

We also engage in patient-advocacy efforts. A large number of Serostim patients have received reimbursement support via our medical reimbursement specialists who work one-on-one with each patient to secure access to and insurance coverage for Serostim once the patient has agreed to receive assistance from our reimbursement specialists. However, during 2004 state-based reimbursers in the United States continued to impose restrictions on the use of Serostim. In some states these restrictions include requiring prescribers to obtain prior authorization before starting a patient on Serostim treatment.

Due to the apparently enlarging gap between demand data and ex-factory sales, we and the relevant authorities initiated investigations to try and discover the cause of this discrepancy. As a result of these investigations, we determined that there were several causes of this discrepancy, including circulation of counterfeit Serostim in the market, potential diversion of the product and an active secondary source for the product in the marketplace. In order to address this issue, we implemented the Serostim Secured Distribution Program, or SSDP, in the United States in October 2002. This program is designed to track and trace Serostim through the distribution process to ensure that patients who require Serostim receive the genuine product on a timely basis. The program restricts distribution of Serostim to a group of contracted network pharmacies that meet predefined criteria and are the exclusive distributors of the product. Through this program we are able to track each individual box of Serostim from Serono to the contracted network pharmacy. We are working closely with individual state and federal agencies to monitor the program’s effectiveness. The FDA recognized SSDP as an effective anti-counterfeiting system that assures patients

receive genuine product.

In 2001, we received FDA approval for a needle-free delivery device for Serostim. This device is called Serojet and was launched in the U.S. market in February 2002.

Gastroenterology

Zorbtive was launched into the U.S. market in May 2004. We promote Zorbtive to gastroenterologists and specialized surgeons. Our efforts are targeted on educating physicians and other patient care providers on the therapeutic benefits of Zorbtive, which is the first drug therapy approved by the FDA for the treatment of Short Bowel Syndrome. We also focus our efforts on educating patients about the therapeutic benefits of Zorbtive and providing support services to assist patients with their therapy.

Zorbtive is also being distributed through the SSDP. We have partnered with our specialty pharmacies to assist in the education process for providers and their patients.

We also engage in patient-advocacy efforts. Zorbtive patients can receive reimbursement support via our medical reimbursement specialists who work one-on-one with each patient to secure access to and insurance coverage for Zorbtive once the patient has agreed to receive assistance from our reimbursement specialists. Zorbtive is currently not available under Medicare.

Dermatology

We have developed a dedicated dermatology sales and marketing structure in our affiliates, consistent with the scheduled launch of Raptiva. Since the beginning of our involvement in dermatology, we have developed strong relationships with key opinion leaders and psoriasis patients associations worldwide.

Manufacturing

Our principal commercial manufacturing facilities are located in Aubonne and Corsier-sur-Vevey, Switzerland; Bari, Italy; Tres Cantos, Spain; and Martillac, France. In 2004, we closed our manufacturing facility in Israel, which was one of our oldest manufacturing sites and had become obsolete. For clinical supplies and process development, manufacturing facilities are located in Martillac, France and Rome, Italy. We have created additional manufacturing centers that specialize in different phases of the production process. For certain key products, we have two production facilities and/or large inventories available to ensure a continuity of supply in the event of contamination, catastrophe or other unforeseen events at one of our facilities.

Intellectual Property

Our patents are very important for protecting our proprietary rights in the products we have developed. We have applied for or received patents covering inventions ranging from basic recombinant DNA to processes relating to production of specific products and to the products themselves. We either have been granted patents or have patent applications pending which relate to a number of current and potential products, including products licensed to others. We believe that in the aggregate our patent applications, patents and licenses under patents owned by third parties are of material importance to our operations.

We expect that litigation will be necessary to determine the validity and scope of certain of our proprietary rights. We have in the past been and may in the future be involved in a number of patent lawsuits, as either a plaintiff or defendant, and in administrative proceedings relating to our patents and those of others. These lawsuits and proceedings may result in a significant commitment of our resources in the future.

We cannot be sure that our patents will give us legal protection against competitors or provide significant proprietary protection or competitive advantage. In addition, we cannot be sure that our patents will not be held invalid or unenforceable by a court, infringed or circumvented by others or that others will not obtain patents that we would need to license or avoid. We are aware that others, including various universities and companies working in the biotechnology field, have also filed patent applications and have been granted patents in the European Union, the United States and other jurisdictions claiming subject matter potentially useful or necessary to our business. Some of those patents and applications claim only specific products or methods of making such products, while others claim more general biotechnology processes or techniques. Competitors or potential competitors may have filed patent applications or received patents, and may obtain additional patents and proprietary rights relating to proteins, compounds or processes competitive with our products.

In general, we have obtained licenses from various parties that we deem to be necessary or desirable for the manufacture, use or sale of our products. These licenses, both exclusive and non-exclusive, generally require us to pay royalties to the parties on product sales.

Trade secret protection for our unpatented confidential and proprietary information is also important to us. To protect our trade secrets, we generally require our employees, material consultants, scientific advisors and parties to collaboration and licensing agreements to execute confidentiality agreements upon the commencement of employment, the consulting relationship or the collaboration or licensing arrangement. However, we cannot be sure that others will not either develop independently the same or similar information or otherwise obtain access to our proprietary information.

We consider the registered (®) and the filed (^{TM}) trademarks and the filed service marks(^{SM}) Canvaxin^{TM}, Cetrotide®, click.easy®, cool.click®, Crinone®, EasyJect®, Fertility LifeLines^{TM}, Ferti.net®, Fertinex®, Geref®, Gonal-f®, GHMonitor ^{SM}, Howkidsgrow ^{SM}, Learning for life^{TM}, Luveris®, Metrodin HP®, MSLifelines ^{SM}, Mylinax®, Novantrone®, one.click®, Ovidrel®, Ovitrelle®, Pergogreen®, Pergonal®, Profasi®, Raptiva®, Rebif®, Rebiject®, Rebiject II®, Rebiject mini®, Reliser®, Saizen®, SeroJet^{TM}, Serono®, Serophene®, Serostim®, Stilamin® and Zorbtive^{TM}, as well as the filed trademarks (^{TM}) for the “S” symbol, used alone or with the words “Serono” or “Serono biotech and beyond,” in the aggregate to be materially important. We have generally registered or are seeking to register these trademarks throughout Europe, in the United States and in other countries throughout the world.

Out-Licensing

Our strength of innovation is evidenced by our strong patent position and our ability to license certain of our technology and rights to third parties. We receive royalties and license fees from a number of companies with respect to their products. Among these are:

- Ÿ Biogen Idec on its sales of Avonex;
- Ÿ Organon on its sales of Puregon and Antagon;
- Ÿ Amgen on its sales of Enbrel; and
- Ÿ Abbott Laboratories on its sales of Humira.

Competition

We face competition, and believe significant long-term competition can be expected, from pharmaceutical companies and pharmaceutical divisions of chemical companies as well as biotechnology companies. We expect this competition to become more intense as commercial applications for biotechnology products increase.

The introduction of new products or the development of new processes by competitors or new information about existing products may result in price reductions or product replacements, even for products protected by patents. In certain markets, such as Latin America, there is limited patent protection available for our products as a result of the historical weakness of the patent law systems. However, we believe our competitive position is enhanced by our commitment to research leading to the discovery and development of new products and manufacturing methods. Other factors which should help us address competition include ancillary services provided to support our products, customer service and dissemination of technical information to prescribers of our products and to the health care community, including payers.

Over the longer term, our and our collaborators' ability to successfully market current products, expand their usage and bring new products to the marketplace will depend on many factors, including but not limited to the effectiveness and safety of the products, regulatory agencies' approvals for new products and indications, the degree of patent protection afforded to particular products, and the effect of the managed care industry as an important purchaser of pharmaceutical products.

Generic Drugs

Generic products are typically sold at a lower price than our products, because producers of generic drugs do not have to incur research and development costs. Therefore, there is increasing pressure on the applicable regulatory entities in both the European Union and the United States to make it easier for pharmaceutical producers to gain approval for generic drugs, including generic recombinant drugs. Our urine-derived reproductive health products, which we are in the final stages of phasing out, already face increased competition from generic products.

Drug Delivery Systems

A growing area of competition in the biotechnology industry results from developments in drug delivery systems - the manner in which drugs are delivered into the human body and the processes by which drugs are time-released into the blood stream once they have been delivered into the human body. Easier and less painful drug delivery systems promote patient compliance and usage and are, therefore, more marketable. Several of our competitors sell autoinjection devices that facilitate self-administration of their treatments. We will face increased competition from drugs that have drug delivery systems that may be more patient-friendly than our own.

Neurology

Rebif and Novantrone are increasingly used in a highly competitive MS marketplace worldwide. In 2004, Rebif was the fastest growing MS treatment in the U.S. and retained market leadership outside the U.S. In the U.S., Rebif and its three competitors faced an additional new competitor, natalizumab (Tysabri), in the last month of 2004. Currently the prescribing label for Rebif is more comprehensive than that of natalizumab as it includes an effect on disability and long-term efficacy data.

Rebif also competes with interferon beta-1b, which is sold by Schering AG or its affiliate Berlex in Europe under the brand name Betaferon and is sold by these companies in the United States and Canada under the name Betaseron. In addition, Rebif competes with Avonex, an interferon beta-1a product sold by Biogen Idec, and with Copaxone, sold by Teva Pharmaceuticals, in the U.S., Europe and other countries. In early 2004, we initiated a head-to-head Phase IV trial comparing Rebif with Copaxone. We announced in January 2005 that recruitment was completed with over 700 patients enrolled. A number of other companies are working to develop products to treat multiple sclerosis that may in the future compete with Rebif.

Another source of competition is the introduction of biosimilar products in Latin America and in Asia. These are not generic versions of Rebif as the exact formulation for Rebif is highly dependent on our well-established manufacturing process. In the U.S. and in Europe the regulatory agencies have so far recognized the need for clinical testing of biosimilar products to establish both efficacy and safety. However, in Latin America (Mexico and Argentina), licenses for biosimilar products were granted in the fourth quarter of 2004. Although the products are not proven and supply may be restricted, we expect there will be some impact on Rebif sales in these regions. Similar developments are not expected in the European Union or U.S. in the near future.

We have exclusive rights to market Novantrone in the United States for advanced forms of MS and have received orphan drug status for Novantrone in these indications. We believe this provides us with a marketing advantage in the United States.

Reproductive Health

Our reproductive health products compete with Organon’s recombinant FSH, Puregon, which is marketed as Follistim in the United States. Our products also compete with urine-derived products, including Ferring Pharmaceutical’s Menopur, Menogon, which is marketed as Repronex in the United States, and Bravelle as well as with Institut Biochimique’s Fostimon and Merional. Ovidrel is currently the only recombinant source of hCG available. However, Ovidrel competes with urine-derived sources of hCG. Luveris is currently the only recombinant source of LH available. In certain markets, Luveris competes with urine-derived human menopausal gonadotropins, which are less pure preparations of FSH and LH. In the United States, Luveris competes with urine-derived human menopausal gonadotropins within its approved indication of hypogonadotropic hypogonadal women with profound LH deficiency. We have received orphan drug protection for Luveris in the United States through October 8, 2011. Crinone competes with other progesterone products; however it is the only preparation available as a non-injectable formulation that is labeled for assisted reproductive technologies, except in the United States where Columbia Laboratories markets

Prochieve to certain obstetricians and gynecologists.

Growth and Metabolism

Growth

Saizen competes with human growth hormone products produced by companies such as Eli Lilly, BioTechnology General, Novo Nordisk, Pfizer and Genentech. The competition in this market is intense because different human growth hormone products are chemically and biologically similar. As a result, it is difficult for one product to differentiate itself. One way that we differentiate our product is through drug delivery systems. However, many of our competitors now also offer patient-friendly delivery systems for their products. Other companies are working to bring to market comparable growth hormone products that may compete with Saizen in the future.

In addition to the presence of competing products in the growth retardation market, we believe that competition in this market is enhanced by the fact that parents show considerable brand loyalty once they have selected a product for treatment of their child. As a result, much of the competition between pharmaceutical companies in this market must focus on the relatively small number of new patients beginning treatment each year.

Metabolism

Orphan drug exclusivity for Serostim in the United States expired in August 2003. Our competitors may now seek approval of applications for their growth hormone products in the United States for AIDS Wasting indications. The appetite stimulants Megace, which is marketed by Par and Roxane, and Marinol, which is marketed by Unimed, and the anabolic steroid Oxandrin, marketed by Savient, are other drugs approved for the treatment of weight loss associated with AIDS or chronic infection in the United States.

Gastroenterology

We have been granted orphan drug exclusivity for Zorbtive in the treatment of patients with short bowel syndrome until December 2010. That means that our competitors cannot receive FDA approval to promote human growth hormone in the United States for that indication until that date.

Dermatology

In psoriasis we currently compete with Enbrel, commercialized by Wyeth, which received regulatory approval in the European Union about one month after Raptiva. In the other markets outside the European Union we currently compete with Amevive from Biogen Idec. Consistent with the product label, traditional systemic therapies or phototherapy are not considered competitors in the European Union markets.

Government Regulation

Our research, preclinical testing, clinical trials, facilities, manufacturing, labeling, pricing and sales and marketing are subject to extensive regulation by numerous governmental authorities in the European Union, the United States, Switzerland and other jurisdictions. The levels of expenditure and the laboratory and clinical information required for regulatory approval are substantial, and obtaining such approval can require a number of years. The results generated through laboratory and clinical studies conducted worldwide may be used in most countries for the registration of products. However, country-specific regulations, such as in Japan, and possible genetic differences among populations may force us to tailor some studies to specific countries, causing additional delays and expense in the registration process. We cannot sell our products in a given jurisdiction without first obtaining regulatory approval to do so. The success of our current and future products will depend in part upon obtaining and maintaining regulatory approval to market them for approved indications in the European Union, the United States and other markets. The regulatory approval process is lengthy and complex in the European Union, the United States and other jurisdictions. We cannot

be sure that we will obtain the required regulatory approvals on a timely basis, if at all, for any of the products we are developing. Even if we obtain regulatory approval, both our manufacturing processes and our marketed products are subject to continued review. Later discovery of previously unknown issues with our products or manufacturing processes may result in restrictions on these processes, and may ultimately lead to withdrawal of the products from the market. Also, new government requirements may be established that could delay or prevent regulatory approval of the products we have in development.

The European Union requires anyone seeking to market a medicinal product for human use to obtain approval of a Marketing Authorization Application, or MAA. Currently, two main regulatory authorization processes coexist in the European Union. Medicinal products of significant therapeutic interest or constituting a significant innovation undergo a centralized assessment procedure for marketing authorizations valid in all European Union member states, which is administered by the European Medicines Agency, or EMEA. This procedure is applicable to drugs that fall within the definition of ‘‘high technology medicines,’’ and includes all new biotechnology products. Under this procedure, the Committee for Human Products, or CHMP, has 210 days, or a longer period if further information is required, to give its opinion as to whether a marketing authorization should be granted. The European marketing authorization is granted after the CHMP opinion has been reviewed and accepted, and the Decision (i.e., the licence) is granted by the European Commission. The single license is valid for the entire European Union. Products that do not qualify for registration under the centralized procedure, or which were registered under a prior system, are still registered nationally, although by a mutual recognition procedure. The regulatory process is complex and involves extensive consultation with the regulatory authorities of the various European Union member states. Issues still exist regarding the right of member states not to mutually recognize licenses granted in other European Union countries due to poorly defined public health concerns, and there can be no assurance that this European process will not introduce delays. Similarly, prior to commercial sale in the United States, all new drugs and new indications for existing drugs must be approved by the FDA. As in the case of the European Union, securing FDA marketing approvals requires the submission of extensive preclinical and clinical data, chemistry, manufacturing and controls information and other relevant supporting information to the FDA. The submitted data should provide sufficient risk and benefit information for the authorities to determine the approvability of the product and indication in terms of its quality, safety and efficacy.

Regulatory approval of pricing and reimbursement is required in most countries outside the United States. For example, regulators in certain European countries condition their reimbursement of a pharmaceutical product on the agreement of the seller not to sell the product for more than a certain price or in more than certain quantities per year in their respective countries. In some cases, the price established in any of these countries may serve as a benchmark in the other countries. As such, the price approved in connection with the first approval obtained in any of these European countries may serve as the maximum price that may be approved in the other European countries. Also, a price approved in one of these European countries that is lower than the price previously approved in the other European countries may require a reduction in the prices in those other European countries. In that event, the resulting prices may be insufficient to generate an acceptable return on our investment in the products.

Manufacturers of drugs also are required to comply with current Good Manufacturing Practice regulations and similar regulations in the countries in which they operate. These include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Manufacturing facilities are subject to inspection by government regulators, including unannounced inspection in their own and other jurisdictions. Most material manufacturing changes to approved drugs also are subject to regulatory review and approval.

We or our suppliers may fail to comply with applicable regulatory requirements such as adverse event reporting, which could lead to product withdrawal or other regulatory action. Serious, unexpected and unlabeled events observed post-marketing worldwide are subject to expedited reporting requirements to the European, U.S. and other health authorities and could result in changes in the “Warnings” and “Precautions” section of the product labeling.

Various laws, regulations and recommendations relating to safe working conditions, Good Laboratory Practices, Good Clinical Practices, the experimental use of animals and the purchase, storage, movement, import and export and use and disposal of hazardous or potentially hazardous materials, including radioactive compounds and infectious disease agents, used in connection with our research work are or may be applicable to our activities. Although we believe that our safety procedures for handling and disposing of hazardous materials comply with the standards prescribed by applicable laws, regulations and recommendations, the risk of accidental contamination or injury from these materials cannot be completely eliminated.

Environmental Regulation

We seek to comply with all applicable statutory and administrative requirements concerning environmental quality. We have made, and will continue to make, expenditures for environmental compliance and protection. Expenditures for compliance with environmental laws have not had, and we do not expect them to have, a material effect on our capital expenditures, results of operation, financial condition or competitive position.

Capital Expenditures, Divestitures and Investments

Our capital expenditure on tangible fixed assets for 2004 totaled approximately $151.5 million, compared to $185.0 million in 2003 and $125.3 million in 2002. This level of capital expenditure reflects our continuing investment in research and development and manufacturing facilities, our investment in our new corporate headquarters and our continuing implementation of advanced information technology systems.

In the fourth quarter of 2003, we took a non-cash charge of CHF 20.8 million or $16.1 million related to the write-down of our 2001 CHF 25.0 million investment in Swiss International Air Lines Ltd. At the end of 2004, the market value of our investment was CHF 4.2 million or $3.4 million and the significant decline in the market value of the investment was considered to be other than temporary.

In the second half of 2002, our subsidiary, Serono France Holding S.A. conducted a tender offer for the outstanding shares of Genset S.A., a French public company. As a result of this tender offer and subsequent open market purchases, as of March 26, 2003, Serono France Holding S.A. had acquired 7,670,863 shares (representing 92.9% of the outstanding shares), 520,431 bonds convertible into new shares (representing 99.7% of such bonds outstanding) and all of the company's outstanding warrants for an aggregate purchase price of $140.1 million. In addition, following the launch by Genset S.A. of a capital increase in March 2003, Serono France Holding S.A. acquired in the market 354,336 subscription rights. The purchase of these rights increased Serono France Holding S.A.'s stake in Genset S.A. to more than 95% of the share capital of Genset S.A., which permitted Serono France Holding S.A. to launch a squeeze-out merger that enabled it to gain control of all of the outstanding equity securities of Genset S.A. in June 2003. As of June 15, 2003, Serono France Holdings S.A. owned 100% of the Genset share capital.

In the first quarter of 2003, we exercised an option to purchase land adjacent to our current headquarters in Geneva in order to construct a facility to support our future growth. This facility will bring together our corporate management and administration and our Switzerland-based research and development in a single location. We estimate that the cost of this project to scheduled completion in 2006 will be approximately CHF371.1 million or $327.7 million which we will substantially finance by means of a credit facility we have entered into. We started construction in the middle of 2003 and this construction is ongoing.

Organizational Structure

We are a holding company for the companies of the Serono group. A listing of our principal operating companies, their country of incorporation and the proportion of our ownership of each can be found in Note 34 of the Notes to Consolidated Financial Statements elsewhere in this Annual Report.

Facilities

We occupy owned or leased facilities in over 40 countries. Our headquarters are located in Geneva, Switzerland. We maintain research and development facilities in Geneva, the Boston area, Evry, France, and Ardea, Italy. Our principal manufacturing facilities are located in Switzerland, Italy, Spain and France. In 2004, we closed our manufacturing facility in Israel, which was one of our oldest manufacturing sites and had become obsolete. We also have leases for additional office facilities in several locations in Europe, North America, Latin America and Asia. We have made and continue to make improvements to our properties to accommodate our growth. We believe our facilities are in good operating condition and that the real property we own or lease is adequate for all present and near-term future uses. We believe that any additional facilities could be obtained or constructed with our existing capital resources.

In 2003, we exercised an option to purchase a 40,000 square meter section of land near our current headquarters in Geneva for the purpose of bringing together on a single site our headquarters and Switzerland-based research and development activities and supporting our anticipated growth. We estimate that the cost of this project to scheduled

completion in 2006 will be approximately CHF371.1 million or $327.7 million. The total costs capitalized as of December 31, 2004 were CHF 161.3 million or $130.4 million. We substantially financed this project by way of a CHF 300 million committed unsecured revolving bank facility. As of December 31, 2004, the amount outstanding under this facility was CHF131.5 million or $116.1 million. The facility is due for repayment on December 31, 2006. In addition, we purchased approximately 31,000 square meters of land in Martillac, France, at a purchase price of $0.1 million, and thereby added to our existing land holdings in Martillac, France. The additional land may be used at a future date to expand our manufacturing production in Martillac.

The following table lists our principal office, research and development and manufacturing facilities**:**

Location	**Use**	**Owned or Leased**	**Size**
Geneva, Switzerland	Headquarters	Leased-Expires 2006	14,578 sq. meters
Geneva, Switzerland	Research and Development	Leased-Expires 2011	12,698 sq. meters
Rockland, Massachusetts, U.S.A.	U.S. Headquarters	Leased-Expires 2016	200,000 sq. feet
Rome, Italy	Italian Headquarters	Owned	10,212 sq. meters
Ardea, Italy	Research and Development	Owned	46.838 sq. meters
Evry, France	Research and Development	Leased-Expires 2005	13,696 sq. meters
Corsier-sur-Vevey, Switzerland	Manufacturing	Owned	36,395 sq. meters
Aubonne, Switzerland	Manufacturing	Owned	43,800 sq. meters
Coinsins, Switzerland	Manufacturing	Owned	19,800 sq. meters
Rome, Italy	Manufacturing, Research and Development	Owned	51,015 sq. meters
Bari, Italy	Manufacturing	Owned	122,150 sq. meters
Tres Cantos, Spain	Manufacturing	Owned	6,028 sq. meters
Martillac, France	Manufacturing	Leased-Expires 2008	1,107 sq. meters
Martillac, France	Manufacturing	Owned	47,683 sq. meters

Item 5. OPERATING AND FINANCIAL REVIEW AND PROSPECTS

You should read the following operating and financial review and prospects in conjunction with the consolidated financial statements and the notes to the consolidated financial statements appearing elsewhere in this Annual Report. We have prepared our consolidated financial statements in accordance with International Financial Reporting Standards (IFRS), which differ in significant respects from United States Generally Accepted Accounting Principles (U.S. GAAP). You can find a reconciliation of the significant differences between IFRS and U.S. GAAP in note 35 to our consolidated financial statements.

Overview

We are a global biotechnology leader with 4,902 employees, worldwide revenues of $2,458.1 million and a net income of $494.2 million in the year 2004. We have eight biotechnology products on the market and a strong pipeline with approximately 30 ongoing development projects, based both on proteins and small molecules.

We use human genetic information to discover, develop and manufacture therapeutic products for the treatment of human diseases. We currently focus on the specialized markets of neurology, reproductive health, growth and metabolism, and dermatology, our newest therapeutic human genetic area.

We are committed to bringing hope to people suffering from multiple sclerosis or MS. Rebif is a treatment for relapsing MS. Several studies support the concept of maximal benefit with higher and more frequent doses of beta-interferon. Rebif 44 mcg, three times per week, has been shown to achieve maximum treatment effect in terms of disease progression and reducing the frequency and severity of relapses.

We are the world leader in the treatment of infertility. Our vision is to develop and market innovative products to help infertile couples at every stage of the reproductive cycle, from follicular development to early pregnancy, in making their dream of having a child come true. We are the only company that uses recombinant technology to produce all three gonadotropin hormones for treatment of infertility and, with a complete portfolio of highly effective fertility drugs that cover every aspect of the reproductive cycle, we offer clinicians the ability to tailor treatment to individual patient needs.

Our goal is to improve and maintain the quality of life of people with metabolic disorders. To meet this goal, we were one of the first to make recombinant growth hormone available for the treatment of Growth Hormone Deficiency in children and adults (Saizen) and for the treatment of patients suffering from AIDS Wasting (Serostim). We continue our commitment to patients with these disorders through these treatments delivered by easy-to-use devices.

We have a global presence with operations in more than 40 countries, production facilities in four countries and sales in over 90 countries. We have spent 24.2% of total revenues on research and development in 2004. We have integrated operations that allow us to manufacture and market the products we derive from our research and development efforts. Our global sales and marketing infrastructure has made us a global partner of choice in the biotechnology industry.

Critical accounting policies and estimates

Our operating and financial review and prospects are based upon our consolidated financial statements, which we prepared in accordance with IFRS. We have provided in note 35 of the consolidated financial statements a reconciliation of net income and shareholders' equity from IFRS to U.S. GAAP. The preparation of financial statements in conformity with IFRS and the reconciliation under U.S. GAAP require us to make estimates and assumptions that affect the amounts we report in the financial statements and accompanying notes. On an ongoing basis, we evaluate our estimates, including those related to reserves for fiscal and legal claims, sales returns, inventory

obsolescence, bad debt reserves and the assessment of impairment of intangible assets and available-for-sale investments, income taxes, pensions and retirement benefit plans. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe the following critical accounting policies affect the more significant judgments and estimates that we use in the preparation of our consolidated financial statements.

Revenue recognition

We recognize revenue from product sales when there is evidence that an arrangement exists, delivery has occurred, the price is fixed and determinable, and collectibility is reasonably assured. Allowances are established for estimated uncollectible amounts, product returns and discounts. We adjust the estimates for returns periodically based upon historical rates of returns, inventory shipment history, estimated levels of product in the distribution channel, and other related factors. While we believe that we can make reliable estimates for these matters, nevertheless unsold products in the distribution channels can be exposed to rapid changes in market conditions or obsolescence due to new competitive environments, product updates or competing products. Accordingly, it is possible that these estimates will change in the near future or that the actual amounts could vary significantly from our estimates.

Assessment of returns

Provisions for sales returns are based on actual historical returns as we feel that this is the best means to estimate future returns of products sold in the current period. The amount of returns we receive varies by region and is dependent upon the return policy within a given country. We perform periodic quantitative analysis by product for each reserve category to assess whether the current assumptions used to calculate the sales return provisions are valid. We calculate a twelve-month rolling return rate based on actual product returns. We then apply this rate against all future outstanding products that could be subject to expiration. The result is the reserve needed for future returns. The reserves that are generated based on the historical rate of actual returns are compared to a qualitative analysis of sales reserves to ensure that the amount of the reserves recorded in our financial statements reflect all of the facts and circumstances that could potentially impact the amount of future returns that we will receive. The qualitative factors that are incorporated into our sales return analysis would include the potential impact on future product returns, for example, of the introduction of a competing product or changes in reimbursement practices.

Assessment of inventory levels in the distribution channel

Our distribution channel includes wholesaler distributors, pharmacies, hospitals and other medical facilities that distribute and/or administer our products. In the U.S. market for example, which accounts for 35.1% of our total product sales, we receive monthly inventory reports from the wholesalers we sell to summarizing by product the amount of inventory held at the end the month. Inventory levels maintained at the wholesalers in the U.S. are approximately 30 days of sales. In Europe, our single largest region, representing 41.1% of our total product sales, we generally maintain inventory levels of less than 30 days. We assess inventory levels maintained in the Europe region based on a comparison of sale volumes to wholesalers against their reported sales to pharmacies, hospitals and other medical facilities.

Throughout all of our regions, wholesalers typically sell to pharmacies, hospitals and other medical facilities. Therefore, there is an additional level of inventory in our distribution channel. However, given the relatively high inventory value of our products and the fact that wholesalers can deliver our products to a healthcare facility on the same day, pharmacies, hospitals and other medical facilities are reluctant to carry significant amounts of our products. Thus we believe that the inventory held at the wholesaler represents the substantial part of the inventory held within the entire distribution channel at any given time.

Assessment of the average age of inventory in the distribution channel

At present time we do not have the ability to track the expiration date of inventory held in the distribution channel on a global basis. Movements in sales reserves during the past three years are summarized in the following table:

	Product returns U.S.$m	Discounts, chargebacks and rebates U.S.$m	**Total sales reserves U.S.$m**
Balance as of January 1, 2002	21.4	23.0	**44.4**
Add: New reserves recorded in 2002	20.0	103.5	**123.5**
Less: Reserves applied during 2002	(20.5)	(94.1)	**(114.6)**
Balance as of December 31, 2002	20.9	32.4	**53.3**
Add: New reserves recorded in 2003	31.1	153.7	**184.8**
Less: Reserves applied during 2003	(15.6)	(132.0)	**(147.6)**
Balance as of December 31, 2003	36.4	54.1	**90.5**
Add: New reserves recorded in 2004	8.8	187.6	**196.4**
Less: Reserves applied during 2004	(15.3)	(187.7)	**(203.0)**
Balance as of December 31, 2004	**29.9**	**54.0**	**83.9**

Gross product sales recorded in 2004, 2003 and 2002 before sales reserves were $2,374.4 million, $2,042.8 million and $1,546.7 million, respectively. New reserves recorded in 2004, 2003, and 2002 as a percentage of gross product sales were 8.3%, 9.0%, and 8.0%, respectively. Reserves for product returns recorded in 2004 were lower when compared to 2003; this was the result of the application of lower product return rates in the U.S. for sales of Rebif and Novantrone. The initial forecasted rates of return that were established upon the launch of these products in the first and fourth quarters of 2002 were estimated without the benefit of historical return data. Return rates for these products were reduced during 2004 based on the volume of actual returns received. In addition, product returns of existing Gonal-f product related to the 2004 U.S. launch of Gonal-f fill-by-mass formulation and the Gonal-f pre-filled pen were less than expected.

Inventory provisions

We write down our inventory by an amount equal to the difference between the cost of inventory and the net realizable value of the inventory, based upon assumptions about future demand and market conditions. If actual market conditions are less favorable than those we project, we may need to take additional inventory write-downs.

Bad debts

We maintain allowances for estimated losses resulting from the inability of our customers to make required payments. If the financial condition of our customers were to deteriorate, resulting in an impairment of their ability to make payments, we might need to make additional allowances.

Impairment testing

We evaluate the carrying value of our tangible and intangible assets for impairment on an annual basis, and also whenever indicators of impairment exist. If we determine that such indicators are present, we prepare a discounted future net cash flow projection for the asset (“value in use”). In preparing this projection, we must make a number of assumptions and estimates concerning such things as future sales performance of our various products and the rates of increase in operating expenses over the remaining useful life of the asset. If the calculation of value in use is in excess of the carrying value of the recorded asset, no impairment is recorded. In the event the carrying value of the asset exceeded the value in use, we would estimate the net selling price of the asset and, where appropriate, we would use the assistance of an external valuation expert. If the carrying value also exceeded the net selling price, we would take

an impairment charge to bring the carrying value down to the higher of net selling price and value in use. The discount rate we use in the calculation represents our best estimate of the risk-adjusted pre-tax rate. Should the sales performance of one or more products be significantly below our estimates, we might have to take an impairment charge on certain tangible assets or intangible assets.

Accounting for available-for-sale investments

We hold available-for-sale investments at fair value and have elected to treat any unrealized gains and losses as increases or decreases in fair value reserves, which affect shareholders' equity. We have a policy in place to review each individual holding of available-for-sale investments at each balance sheet date to evaluate whether or not each investment is permanently impaired. Our policy includes reviewing all publicly available information provided by the company in which we have invested and analysts' reports for evidence of significant financial difficulty, recognition of impairment losses, possibility of bankruptcy, severe operational setbacks and other impairment indicators. If we believe that a permanent impairment has been incurred and the eventual recoverable amount will not exceed the original cost, it is our policy to recognize an impairment loss in the income statement.

Deferred income taxes

We account for deferred income taxes based upon differences between the financial reporting and income tax bases of our assets and liabilities. We record deferred tax assets only to the extent that it is probable that taxable profit will be available in the affiliate that has recognized the deferred tax assets, which is an assessment that is based on management judgment.

Pensions

Substantially all of our employees are covered by defined benefit, defined contribution, insured or state pension plans. The expense incurred under the defined benefit retirement plans is based upon statistical and actuarial calculations, and is impacted by assumptions on discount rates used to arrive at the present value of future pension liabilities, expected returns that will be made on existing pension assets, future salary increases as well as future pension increases. Furthermore, our independent actuaries use statistical based assumptions covering future withdrawals of participants from the plan and estimates on life expectancy. The actuarial assumptions used may differ materially from actual results due to changes in market and economic conditions, higher or lower withdrawal rates or longer or shorter life spans of participants. These differences could impact significantly the amount of pension income or expense recognized in future periods.

Contingencies

Several of our subsidiaries are parties to various legal proceedings including possible breach of contract, patent infringement cases and other matters. As a result, claims could be made against them which might not be covered by existing provisions or by insurance. There can be no assurance that there will not be an increase in the scope of these matters or that any future lawsuits, claims, proceedings or investigations will not be material. Management believes that during the next few years, the aggregate impact, beyond current reserves, of these and other legal matters affecting the company is reasonably likely to be material to the company's results of operations and cash flows, and may be material to its financial condition and liquidity.

Results of operations – Overview

We are active in the research, development, production and marketing of products that address our four current therapeutic areas of neurology, reproductive health, growth and metabolism and dermatology.

Total revenues

Product sales

In 2004, five products accounted for 92.6% of our total product sales. Rebif, our largest selling product accounted for 50.1% of our sales, is a recombinant interferon beta-1a that we sell for the treatment of multiple sclerosis. Gonal-f, our second largest selling product accounted for 26.3% of our product sales, is a recombinant human follicle stimulating hormone that we sell for the treatment of infertility. Saizen and Serostim are different formulations of recombinant human growth hormone, and are our third and fourth largest selling products, respectively and on a combined basis, accounted for 12.3% of our product sales. Saizen is used in the treatment of growth retardation due to a variety of causes. Serostim is used to treat AIDS Wasting. Novantrone, for which we purchased the marketing rights to sell in the U.S. market, is indicated for certain types of worsening MS and also for certain forms of cancer. Product sales of Novantrone for the two separate indications are reported under our neurology therapeutic area and as other product sales, respectively and accounted for 3.9% of our total product sales. In addition to the main products highlighted above, we also sell a variety of other products.

Royalty and license income

We currently receive ongoing royalties under licensing agreements with Biogen Idec for its sales of Avonex, Organon for its sales of Puregon, Amgen for its sales of Enbrel and Abbott Laboratories for its sales of Humira. Our revenues from these agreements increase or decrease in proportion to our licensees' sales of their products. We derive license income from licensing our intellectual property to third parties. In addition, we also receive non-recurring amounts through patent settlements with third parties.

Operating expenses

Our operating expenses are composed of cost of product sales, selling, general and administrative expenses, research and development expenses, and other operating expenses.

Cost of product sales

Cost of product sales includes all costs we incur to manufacture the products we sell in a given year. Our largest components of cost of product sales are employee-related expenses, depreciation of manufacturing plant, property and equipment, materials and supplies, utilities and other manufacturing-related facility expenses. We also purchase directly from outside manufacturers finished products including Raptiva, Crinone and Cetrotide, that we sell as part of in-licensing agreements that grant us exclusive rights to sell these products in specific territories. The payments that we make to our in-licensing partners are capitalized as intangible assets and amortized over the shorter of the term of the license and the period in which we expect to sell the in-licensed product. Amortization expense is reported under other operating expense.

Selling, general and administrative

Our selling, general and administrative expenses are composed of distribution, selling and marketing and general and administrative expenses:

Distribution. In general, we sell our products to wholesale distributors or directly to hospitals, medical centers and pharmacies. Distribution expenses are primarily freight expenses, employee-related expenses and expenses incurred by third-party distributors in distributing our products.

Selling and marketing. We maintained a marketing and sales force of 2,084 employees in 2004 to sell or manage the distribution of our products in almost 100 countries. Our selling and marketing expenditures consist primarily of employee-related expenses and costs associated with congresses, exhibitions and advertising as well as commissions paid to our two co-promotion partners: Pfizer, which co-promotes Rebif in the U.S. market, and OSI Pharmaceuticals, which co-promotes Novantrone in the U.S. as a treatment for certain forms of cancer.

Selling and marketing expense generally maintains a positive correlation with the volume of products that we sell. However, we may incur additional selling and marketing expense upon the introduction of a new product or when we introduce existing products into new markets, as we hire additional sales personnel to undertake product launches. For example, we received European Commission Marketing Authorization for Raptiva (efalizumab) for the treatment of adult patients with moderate to severe chronic plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including cyclosporine, methotrexate and PUVA. Raptiva is the first new biological treatment for psoriasis to be authorized for marketing in the European Union. Raptiva was available in 15 countries including Germany and UK by the end of 2004 and will launch throughout the rest of the Serono territories during 2005. The cost of the launch of Raptiva contributed to the increase in reported selling and marketing expense expressed as a percentage of product sales.

General and administrative. We incur general and administrative expenses in maintaining our headquarters in Geneva and our operations in more than 40 countries. We centralize certain functions, such as finance, information technology, treasury, tax and legal, to the extent possible, to achieve economies of scale in operations.

Research and development

Research and development or R&D is one of our key functions, and we employed 1,387 R&D employees in 2004. We incur our primary R&D expenses in connection with the operation of the Serono Pharmaceutical Research Institute in Geneva, the Serono Reproductive Biology Institute in Boston, the Istituto di Ricerca Cesare Serono, which merged into the Industria Farmaceutica Serono, the Istituto di Ricerche Biomediche ‘‘Antoine Marxer’’ RBM in Italy, the Serono Genetics Institute in France, Bourn Hall in UK and our corporate R&D organization.

We also invest significantly in collaborations with other biotechnology companies that can require material up-front payments, future ongoing milestone payments, and eventually future royalty payments that are normally based on a percentage of sales we generate from a product that we have in-licensed. In most cases, up-front and milestone payments, payable under research and development agreements, are charged directly to research and development expense, unless there is significant evidence that all of the criteria for capitalization, as prescribed by IAS 38, “Intangible Assets”, are met. Acquired projects which have achieved technical feasibility, usually signified by regulatory body approval, are capitalized, as it is probable that the costs will give rise to future economic benefits. During 2004, we incurred $83.7 million in collaborative payments that have been recognized as research and development expense, as they did not meet the criteria for capitalization.

On January 1, 2005, we will adopt IAS 38 (revised 2004), “Intangible Assets”, which will have a material impact on the accounting for our collaborative arrangements. This standard recognizes that the price that we pay to acquire an intangible asset as part of an in-licensing agreement reflects expectations about the probability that the expected future economic benefits from the asset will flow to us. The effect of probability is reflected in the cost of the asset. The probability recognition criterion is always considered to be satisfied for separately acquired intangible assets. We expect that the adoption of this standard in 2005 will result in an increase in the amount of capitalized intangible assets. This revised standard is to be applied prospectively. Therefore, the accounting for the transactions made prior to January 1, 2005, will not be amended by this revised standard.

The adoption of IAS 38 (revised 2004), “Intangible Assets”, in fiscal year 2005 will result in a significant difference between IFRS and U.S. GAAP as intangible assets acquired as part of a separate transaction will continue to be expensed under U.S. GAAP until the asset has achieved technical feasibility which is usually signified by regulatory approval. The difference that will be included in our reconciliation from IFRS to U.S. GAAP will be equal to the amount of payments that we make to acquire intangible assets that are part of separate transactions, that have been capitalized as intangible assets and that have not achieved technical feasibility at the time of the transaction. This difference will be deducted from our reported net income in accordance with IFRS to arrive at net income reported under U.S. GAAP. Had IAS 38 (revised 2004), “Intangible Assets”, been effective on January 1, 2004, reported research and development expense for the year ended December 31, 2004, would have been lower by $83.7 million.

Other operating expense

Other operating expense includes royalty and license expense, amortization of intangibles and other long-term assets, litigations and legal costs, patent and trademark expenses, and equity compensation expenses related to our Employee Share Purchase Plan.

We incur the majority of our royalty and licensing expenses under agreements that we have with Amgen and Wyeth on sales of Novantrone; Genentech on sales of Raptiva; Yeda, the commercial arm of the Weizmann Institute in Israel, on royalties received from Biogen, Amgen and Abbott Laboratories and also on sales of Rebif; Columbia University on sales of Gonal-f; Roche on sales of Rebif; and Berlex Laboratories Inc., the U.S. subsidiary of the Schering Group, on sales of Rebif. Our expenses under these licenses vary with the royalties received and the sales of the applicable products.

On January 1, 2005, we will adopt IFRS 2, “Share-Based Payments”, which will require us to expense the fair value of stock options granted to employees and directors. The application of this new standard requires that all stock options that were granted after November 7, 2002 and had not vested before January 1, 2005 must be expensed over their vesting period. Therefore, in 2005, being the first period that we will expense the fair value of stock options, we will adjust our 2004 reported results to reflect additional operating expense in the amount of $12.2 million before tax.

Year ended December 31, 2004 compared to year ended December 31, 2003

The following compares our results in the year ended December 31, 2004 to those of the year ended December 31, 2003. Our analysis is presented as follows:

1. Overview
2. Product sales by therapeutic area
3. Product sales by region
4. Operating expenses to net income

1. Overview

Our total revenues increased by 21.8% to $2,458.1 million during 2004. Our total revenue growth in local currencies was approximately 16.1%, reflecting our strong underlying growth. Worldwide product sales were $2,177.9 million in 2004, representing an increase for the year of 17.2%. Product sales growth in local currencies was 11.5% in 2004. The total currency impact on reported product sales and total revenues was $100.1 million or 4.6% and $107.4 or 4.4%, respectively.

Royalty and licensing income increased by 74.4% to $280.1 million for the year and was impacted by a new license agreement under a non-core technology that was granted during the year and for which we recognized $67.0 million in license income. The license fee is payable in equal annual installments over the next three years. However, the full amount of the license fee was recognized as royalty and license income in 2004 as no further performance obligation exists on our behalf.

Our royalty income increased by 19.8% to $188.7 million during the year and reflects our strong intellectual property rights. The increase was due to higher royalty income received from Abbott Laboratories on its sales of Humira; from Amgen on its sales of Enbrel and from Biogen Idec on its sales of Avonex.

Operating expenses increased by 22.1% to $1,933.9 million or 78.7% of total revenues. Our operating expenses were unfavorably impacted by the weakening of the U.S. dollar against most major currencies and in particular the Swiss franc and Euro. The total estimated currency impact on reported operating expenses was $85.7 million or 4.4%. Our operating margin was 21.3% compared to 21.5% in 2003. Our operating margin, after removing the currency impact, was 21.4%.

Net income increased by $104.2 million or 26.7% and represents 20.1% of total revenues. Our reported net income benefited from a net favorable currency impact of $17.2 million or 3.5%. Basic earnings per bearer shares increased by 31.3% from $24.63 in 2003 to $32.35 in 2004.

Our outlook for 2005 includes sales growth of between 10% and 15%, total 2005 revenues of at least $2.6 billion and net income of between $520 million and $540 million all based on prevailing currency exchange rates.

2. Product sales by therapeutic area

The following tables summarize, for the periods indicated, our product sales by therapeutic area:

	Year ended December 31,				
	2004 U.S. $m	Change in %	2003 U.S. $m	Change in %	2002 U.S.$m
Neurology					
Rebif	**1,090.6**	33.1	819.3	49.3	548.8
Novantrone	**32.4**	5.0	30.9	10,166.7	0.3
Total neurology	**1,123.0**	32.1	850.2	54.9	549.1
Reproductive health					
Gonal-f	**572.7**	8.7	526.9	17.0	450.4
Cetrotide	**24.8**	(0.2)	24.8	35.3	18.4
Crinone	**19.8**	(4.6)	20.8	90.2	10.9
Ovidrel	**17.7**	43.3	12.4	117.2	5.7
Luveris	**10.6**	6.0	10.0	52.4	6.6
Core infertility portfolio	**645.6**	8.5	594.9	20.9	492.0
Metrodin HP	**15.9**	(36.0)	24.8	(50.6)	50.1
Pergonal	**11.5**	(74.9)	45.8	(0.4)	46.0
Profasi	**6.7**	(56.2)	15.4	(22.4)	19.8
Other products	**12.6**	4.9	12.0	(13.4)	14.0
Total reproductive health	**692.3**	(0.1)	692.9	11.4	621.9
Growth and metabolism					
Saizen	**182.1**	20.2	151.5	22.1	124.0
Serostim	**86.8**	(2.2)	88.7	(6.6)	95.1
Zorbtive	**0.9**	-	-	-	-
Total growth and metabolism	**269.8**	12.3	240.2	9.6	219.1
Dermatology					
Raptiva	**4.9**	-	-	-	-
Total dermatology	**4.9**	-	-	-	-
Other products	**87.9**	17.8	74.7	125.5	33.0
Total product sales	**2,177.9**	17.2	1,858.0	30.6	1,423.1
Recombinant products	**1,961.7**	21.9	1,609.4	30.7	1,231.3
Non-recombinant products	**216.2**	(13.0)	248.6	29.7	191.8

Neurology

In 2004, neurology sales were up 32.1% to $1,123.0 million, reflecting the continued strong demand for Rebif, with a significant market share increase. Rebif achieved blockbuster status reaching over one billion U.S. dollars in annual worldwide sales in 2004. Worldwide sales of Rebif increased by 33.1% to $1,090.6 million in 2004, compared to $819.3 million last year. In local currencies, Rebif sales increased by 25.4%. Sales growth was driven by a

combination of a volume increase of 29.0% and a 3.2% increase in average selling price on account of sales denominated in currencies other than U.S. dollar. When holding exchange rates constant, our average selling price decreased by 2.8%, mostly due to pressure on prices, particularly in the European Union.

Rebif sales in the U.S. increased by 56.8% in 2004 to reach $295.6 million, compared to $188.5 million in 2003 reflecting the continued strong demand.

Rebif sales in Europe grew by 25.6% to $531.7 million compared to $423.2 million in 2003. In local currencies, sales increased by 13.7%. This was primarily driven by increased patient market share in Italy, Spain, and France and a growing patient base in the UK following an increase in the funding from health authorities.

Rebif sales in Latin America increased by 23.8% to $75.9 million in 2004 compared to $61.3 million in 2003, primarily due to higher sales in Brazil, Venezuela and Argentina.

Rebif sales in the rest of the world grew by 28.0% (or 21.2% in local currencies) to $187.4 million compared to $146.3 million in 2003 driven by strong sales in the Middle East, Central Europe and Switzerland as well as the emerging markets of Bulgaria and Romania.

For the twelve months ended September 2004, our worldwide dollar market share reached 24.1%, up 1.7% compared to the same period last year. Excluding sales in the U.S., our dollar market share was 35.5%, down 0.3% compared to the same period in 2003. In the U.S., our dollar market share reached 12.6% as of September 30, 2004 compared to 9.7% one year earlier.

Reproductive health

Reproductive health or RH product sales were $692.3 million during 2004 compared to $692.9 million in 2003. In local currencies, RH product sales decreased by 4.7%. Our RH core infertility portfolio made up of three recombinant hormones (Gonal-f, Ovidrel, Luveris) and two supporting products (Cetrotide, Crinone) grew by 8.5% (or 3.4% in local currencies) from $594.9 million in 2003 to $645.6 million in 2004.

In 2004, difficult market conditions, primarily in Europe, impacted our RH franchise performance. The implementation of healthcare reforms in Germany at the beginning of the year reduced pricing and reimbursement levels. However, we have seen a good performance in other regions beginning with the U.S., where recombinant market share increased, though this was partially offset by the phase-out of Pergonal as of March 2004. We had market share gains in Spain and a successful launch of the Gonal-f pen in Oceania and strong sales growth in Middle East, Africa and Eastern Europe.

Our sales of Gonal-f increased by 8.7% to $572.7 million in 2004 from $526.9 million in 2003 or by 3.6% in local currencies. Sales growth of Gonal-f was driven by a volume increase of 5.2% and an increase in the average selling price of 3.4% due to both currency and regional sales mix. After removing the favorable impact of foreign currency, the average selling price decreased by 1.5% during 2004. The growth in volumes was largely due to the increasing penetration of our multidose presentation and the launch of our fill-by-mass formulation and Gonal-f pre-filled pen.

The sales growth of Gonal-f was achieved despite the adverse impact of the German healthcare reform that took effect on January 1, 2004. Gonal-f sales in Germany have decreased during the year by $36.2 million.

Ovidrel sales increased by 43.3% to $17.7 million compared to $12.4 million in 2003. In the same period, Luveris sales increased by 6.0% to $10.6 million. Recombinant gonadotropin sales as a percentage of total gonadotropin sales increased from 86.0% in 2003 to 94.0% this year. Urine-derived gonadotropins sales decreased by 57.2% from $89.3 million in 2003 to $38.2 million in 2004. Metrodin HP sales declined by 36.0% from $24.8 million in 2003 to $15.9 million this year. In line with our strategy to phase out Pergonal in 2004, its sales continued to decrease from $45.8 million in 2003 to $11.5 million this year.

Sales of Crinone decreased by 4.6% (or 7.8% in local currencies) to $19.8 million compared to $20.8 million in 2003. Sales of Cetrotide were slightly below last year, down 0.2% (or 5.4% in local currencies), at $24.8 million in 2004.

Growth and metabolism

Our growth and metabolism product sales increased by 12.3% to $269.8 million in 2004 from $240.2 million in 2003. In local currencies, product sales increased by 8.2%. Sales of Saizen increased by 20.2% to $182.1 million in 2004 from $151.5 million in 2003 or by 13.6% in local currencies. Sales growth resulted from strong demand in the U.S.

market and also in Asia Pacific, mostly in Korea and Taiwan, as well as in Middle East, Africa and Eastern Europe. Volumes and average selling price increased by 16.7% and 3.0%, respectively during the year. After removing the favorable impact of foreign currency, the average selling price decreased by 2.6%.

Serostim sales in AIDS Wasting were $86.8 million in 2004, down 2.2% compared to 2003, reflecting the slight decrease in Serostim demand in the U.S.

Dermatology

We received European Commission Marketing Authorization for Raptiva (efalizumab) for the treatment of adult patients with moderate to severe chronic plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including cyclosporine, methotrexate and PUVA. Raptiva is the first new biological treatment for psoriasis to be authorized for marketing in the European Union. We launched Raptiva in 15 countries including Germany and UK during the 2004 and will launch throughout the rest of the Serono territories during 2005. Product sales of Raptiva in 2004 were $4.9 million.

3. Product sales by region

The following tables summarize, for the periods indicated, our product sales by region:

	Year ended December 31,				
	2004 U.S.$m	Change in %	2003 U.S.$m	Change in %	2002 U.S.$m
Europe	**895.2**	12.3	796.8	28.4	620.4
North America	**837.9**	20.7	694.3	44.8	479.6
Middle East, Africa and Eastern Europe	**196.3**	29.8	151.2	40.5	107.6
Asia-Pacific, Oceania and Japan	**137.5**	17.6	116.9	10.1	106.3
Latin America	**111.0**	12.4	98.8	(9.5)	109.2
Total product sales	**2,177.9**	17.2	1,858.0	30.6	1,423.1

Europe

Sales in Europe for the year 2004 increased by 12.3% to $895.2 million compared to $796.8 million in 2003. In local currencies, sales increased by 1.7%. This result was primarily due to increased sales of Rebif in almost all European countries, up 13.7% in local currencies. Our RH core infertility portfolio was down 14.5% primarily from the decrease in sales of Gonal-f in Germany as a result of healthcare reform that was enacted on January 1, 2004. Gonal-f sales in Germany decreased by $36.2 million during the year.

North America

Sales in North America increased by 20.7% in 2004 to $837.9 million. Sales growth in this region was primarily within the U.S. due to the strong performance of Rebif (up 56.8%), Gonal-f (up 13.2%), Saizen (up 24.0%), and Novantrone (up 8.8%). This was partially offset by lower sales of Pergonal as it was phased-out of the U.S. market as of March 2004, down 79.9%.

Middle East, Africa and Eastern Europe

In the Middle East, Africa and Eastern Europe, sales increased by 29.8% to $196.3 million due to the strong performance of Rebif, the RH core infertility portfolio and Saizen, partially offset by decreased sales of Pergonal, Profasi and Metrodin HP.

Asia-Pacific, Oceania and Japan

Sales in Asia-Pacific were $65.1 million, up 6.8% (or 5.5% in local currencies) primarily driven by increased sales of Gonal-f and Saizen up 15.2% and 59.2%, respectively, partially offset by decreased sales of Metrodin HP, Pergonal and Profasi. Sales in Oceania increased by 39.2% (or 22.5% in local currencies) to $40.2 million, primarily attributable to higher sales of the RH core infertility portfolio products. In Japan, sales increased by 18.7% (or 10.4% in local currencies) to reach $32.1 million mainly attributable to higher sales of Saizen, Pergogreen and Serostim.

Latin America

Sales in Latin America increased by 12.4% to $111.0 million primarily driven by strong Rebif sales performance, up 23.8% and the RH core infertility portfolio, up 16.2%. This was partially offset by lower Pergonal sales down 98.3%.

Royalty and license income

	Year ended December 31,				
	2004	Change	2003	Change	2002
	U.S.$m	in %	U.S.$m	in %	U.S.$m
Royalty and license income	**280.1**	74.4	160.6	40.0	114.7

Our royalty and license income increased by 74.4% (or 69.5% in local currencies) to $280.1 million in 2004 compared to $160.6 million in 2003. They were impacted by a new license agreement for a non-core technology that was granted during the year for which we recognized $67.0 million in license income. The license fee is payable in equal annual installments over the next three years. However, the full amount of the license fee was recognized as royalty and license income in 2004 as no further performance obligation exists on our behalf.

Our royalty income increased by 19.8% to $188.7 million during the year compared to $157.5 million in 2003 and reflects our strong intellectual property rights. This increase was due to higher royalty income received from Abbott on its sales of Humira, Amgen on its sales of Enbrel, and Biogen Idec on its sales of Avonex. This was partially offset by a decrease in royalty income earned from Organon on its sales of Puregon, and a number of other products.

4. Operating expenses to net income

Cost of product sales

Cost of product sales in 2004 increased by 8.8% to $304.1 million from $279.6 million in 2003. Cost of product sales as a percentage of product sales decreased to 14.0% from 15.0% in the prior year. The corresponding gross margin percentage was 86.0% in 2004, compared to 85.0% last year. Our gross margin in 2004 includes the impact of closing our manufacturing operation in Israel that resulted in a one-time charge of $20.5 million related to people costs and the write-down of tangible fixed assets. Our gross margin percentage without the impact of these closure costs would have been 87.0%.

The increase in gross margin was primarily the result of favorable changes in product mix and continuing manufacturing productivity gains leading to higher production yields. However, this was partially offset by the strength of the Swiss franc and Euro against the U.S. dollar during 2004, as our costs of manufacturing are incurred in Swiss franc and Euro. Our reported product sales benefited from sales denominated in non-U.S. dollar currencies resulting in a favorable currency impact in 2004 of $100.1 million while cost of product sales was adversely impacted by an unfavorable currency impact of $14.3 million.

The proportion of recombinant products sales reached an all time high in 2004 of 90.1%. This proportion is expected to level off upon the completion of our final phase out of our urinary products combined with our launch of Raptiva outside the U.S. and Japan. Gross margin is expected to continue to benefit in the near term from continued economies of scale and the expected utilization of some of our spare manufacturing capacity. We expect that gross margin will reach 88% within the next two years.

Selling, general and administrative

	Year ended December 31,				
	2004 U.S.$m	Change in %	2003 U.S.$m	Change in %	2002 U.S.$m
Selling and marketing	**612.5**	29.5	472.9	25.4	377.1
General and administrative	**195.4**	19.3	163.9	28.9	127.1
Total selling, general and administrative	**807.9**	26.9	636.8	26.3	504.2

Selling and marketing expenses were $612.5 million, or 24.9% of total revenues in 2004 compared to $472.9 million for last year, corresponding to an increase of 29.5%. This increase in reported selling and marketing expenses was mainly driven by higher sales commissions incurred on sales of Rebif and Novantrone in the U.S., sales and marketing costs associated with the launch of Raptiva, and marketing activities to support our product sales growth including Gonal-f filled-by-mass and Gonal-f pre-filled pen.

General and administrative expenses were $195.4 million or 8.0% of revenues in 2004 compared to $163.9 million in 2003, which represents an increase of 19.3%. This increase was primarily due to increased personnel related costs and facility expenses.

Our reported selling, general and administrative expenses include an unfavorable currency impact of $36.6 million or 4.5% primarily due to the strength of the Euro and Swiss franc compared to the U.S. dollar.

Research and development

	Year ended December 31,				
	2004 U.S.$m	Change in %	2003 U.S.$m	Change in %	2002 U.S.$m
Research and development	**594.8**	27.1	467.8	30.6	358.1
Research and development as a % of revenues	**24.2**		23.2		23.3

Research and development expenses in 2004 reached $594.8 million, or 24.2% of total revenues, compared to $467.8 million, or 23.2% of total revenues, in 2003. Research and development expenses include the costs of several key new collaborative and license agreements that were signed with ZymoGenetics Inc., CancerVax Corporation and Micromet AG. We also continued to invest substantially in the pharmaceutical development of new molecules, most notably onercept and TACI-lg. There were also significant investments in clinical development projects aimed at the development of onercept in psoriasis, Serostim for HARS in the U.S., the Raptiva study supporting the New Drug Application in Europe, which was granted in the third quarter of 2004, and the Rebif vs. Copaxone head-to-head study. Finally there were significant additional investments made in the discovery area, mainly in functional genomics aimed at identifying novel therapeutics proteins from the human genome, and the genetics work in the field of autoimmune diseases at the Serono Genetics Institute.

Other operating expense, net

Other operating expenses, net were $227.1 million in 2004 compared to $199.5 million in 2003, corresponding to an increase of 13.8% or 13.2% in local currencies. This increase was due to higher ongoing royalty expenses that were driven by higher sales of Rebif and additional royalty expenses related to royalty income received for Humira, Enbrel and Avonex.

Operating income

Our operating income increased by 20.5% to $524.1 million in 2004 from $434.9 million in 2003. As a percentage of total revenues, our operating income was 21.3% in 2004 compared to 21.5% in 2003.

Financial income, net

	Year ended December 31,				
	2004 U.S.$m	Change in %	2003 U.S.$m	Change in %	2002 U.S.$m
Financial income	**68.2**	36.8	49.8	(22.9)	64.6
Financial expense	**(24.0)**	85.4	(13.0)	21.7	(10.6)
Foreign currency gains/(losses)	**19.1**	167.1	7.2	140.8	(17.5