BIOHIT

ANNUAL REPORT

2003




Humming Bird

The qualities of the humming bird symbolize Biohit's product ranges of liquid handling, diagnostics, instruments, service and complete analyzing systems composed of these product groups.

Biohit's products are characterized by excellence in the selected areas of specialization and performance: versatility, flexibility, power, speed, light weight, design, ergonomics, accuracy and precision as well as safety in delicate operations.

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OVERVIEW ON BIOHIT IN 2003

Biohit concentrates solely on those business areas in which it possesses knowledge of the customer and market needs as well as a strong basis on research, technological know-how, innovations and products protected by patents[1,2]. Biohit develops and manufactures liquid handling products and diagnostic test systems for use in health care, research and industrial laboratories.

The liquid handling product range developed and manufactured by Biohit covers electronic and mechanical pipettors, and disposable tips. The range offered by the company is currently the widest in the world. Biohit is the global market leader of electronic pipettors, and the leading manufacturer of OEM[3] -electronic pipettors in the world.

In the area of diagnostics Biohit develops and manufactures enzyme immunoassay (EIA) -based test kits and monoclonal antibodies for the screening of different types of diseases. Biohit possesses numerous hybridomas[4] for the for the production of monoclonal antibodies[5] Biohit's new diagnostic product range comprises a test panel (GastroPanel) for diagnosing *Helicobacter pylori*[6] -infection and atrophic gastritis[7] as well as for screening the risk of gastric cancer, peptic ulcer, the reflux disease[8], and is complication, Barrett´s oesophagus[9] from a blood sample.

The GastroPanel-examination and the GastroSoft-program interpreting the results of the GastroPanel enable to replace invasive gastroscopy as an initial method when examining patients suffering from stomach pains and discomfort. In the area of diagnostics Biohit offers also tests for the detection of systemic lupus erythematosus (SLE)[10] and lactose intolerance[11].

The product range of Biohit covers, in addition to liquid handling products and diagnostics, instruments used for the analyses of test results. Moreover, Biohit offers maintenance, calibration and training services.

The production plants of Biohit are located in Kajaani and Helsinki, Finland. The sales and marketing subsidiaries are located in China (representative office), France, Germany, Japan, Russia, the U.K. and the U.S. The global distributor network of Biohit covers altogether approx. 450 members in 70 countries. Biohit cooperates with companies such as Beckman Coulter, Becton Dickinson, bioMérieux, Johnson & Johnson Group and 3M.

In 2003 the group net sales of MEUR 26.3 was generated primarily by the sales of liquid handling products and maintenance services. The degree of domestic production totalled 95%. Exports accounted for 94% of the group net sales. In 2003 altogether 57.4% of the net sales was generated in Europe, 21.0% in the Americas, 13.3 % in Asia, and 8.3% in other countries.

In 2003 the turnover of the B-share of Biohit (BIOBV) at the Helsinki Exchanges was EUR 2,382,014 and 1,287,467 in pieces. The highest price was EUR 3.30, the lowest EUR 1.22, and the average price EUR 1.85. The closing price at the end of 2003 was EUR 2.50. The market capitalization value was EUR 22,655,318. Biohit listed on the New Market (NM) -list of the Helsinki Exchanges in 1999.

Mission of Biohit

The mission of Biohit is to create such innovations and products, which promote the well-being of persons and the quality of life. In order to achieve this mission Biohit continues to focus on those business areas in which it possesses a solid multidisciplinary background in the areas of research, technology, innovations and patented products.

The mission of Biohit lies on an aggressive innovation and patenting strategy. In pursuing the said strategy the management and numerous key persons have acted as pioneers and examples for many small and large companies as of the 1970s. This foundation forms the basis for the development of products, which promote efficient and safe laboratory practice, decentralized laboratory diagnostics and related targeted treatment (evidence-based medicine).

Vision of Biohit

The vision of Biohit for the following five years is:

Liquid Handling
- Maintain the position as the leading manufacturer of electronic liquid handling devices in the world
- Become the leading manufacturer of mechanical liquid handling devices
- Develop the business area and market segments of liquid handling instruments, which are based on the know-how, innovations and technology developed by the company

Diagnostics and Diagnostic Analyzing Systems
- Benefit from the potential of the diagnostic tests by using the following marketing channels: Subsidiaries of Biohit, distributors, potential strategic alliances and licensing. Moreover, develop possibly a joint venture with a multinational company possessing a strong marketing network.

1 In January 2000 Biohit, as the first biotechnology company listed on the NM-list of the Helsinki Exchanges, possessed 16 Finnish patents and 31 patent applications. At that time the twenty other companies having recently listed possessed altogether 11 patents and 24 patent applications (Board of Patents and Registration, Taloussanomat January 26, 2000). By the end of December 2003 Biohit possessed 28 Finnish patents and 9 patent applications.
2 Yksityislääkäri (2003). Aggressive Innovation and Patenting Strategy as a Means for Success (in Finnish). No. 1: 96-98.
3 Original Equipment Manufacturer refers to products which are tailor-made according to customer specifications.
4 Somatic cell hybrid formed by a fusion of cells.
5 Milstein and Köhler received the Nobel prize for inventing monoclonal antibodies in 1984.
6 *Helicobacter pylori* (*H. pylori*) causes atrophic gastritis and is related with the development of gastric cancer and peptic ulcer.
7 Atrophic gastritis refers to a loss of normal mucosal glands of the stomach, which is caused by prolonged *H. pylori* -infection. *H. pylori* -infection causes always an inflammation (gastritis) in the stomach.
8 The oesophageal reflux disease refers to a condition in which a reflow of the gastric juice occurs. This may cause the following symptoms: Regurgitation, heartburn and the development of acidity in the stomach.
9 Barrett's oesophagus results from of a long-term reflux disease, which may lead to oesophageal cancer.
10 Systemic lupus erythematosus (SLE) is a connective tissue disease which resembles rheumatic diseases.
11 Lactose intolerance is caused by the lack of the lactase enzyme, which breaks down milk sugar (lactose) in the mucosa of the small intestine.

Key Financial Indicators of the Biohit Group

(EUR 1000 unless stated otherwise)	1999	2000	2001	2002	2003
Net sales	20 551	24 247	25 545	25 354	26 259
Change in net sales, %	21.7	18.0	5.4	-0.7	3.6
Return on equity, %	3.8	-4.6	-1.3	-11.7	-4.9
Return on investment, %	8.5	-0.8	2.0	-5.5	-1.3
Equity ratio, %	66.0	66.9	65.7	66.9	64.7
Investments in fixed assets	1 271	6 208	2 212	1 578	1 190
% of net sales	6.2	25.6	8.7	6.2	4.5
Research and development expenses	1 270	1 698	2 114	1 809	1 447
% of net sales	6.2	7.0	8.3	7.1	5.5
Personnel, average	184	222	289	303	298

Share Capital, Shares and Key Rations

	1999	2000	2001	2002	2003
Number of shares, end of fiscal year	12 264 537	12 643 377	12 643 377	12 937 627	12 937 627
Key ratios					
Earnings per share (EPS), EUR	0.04	-0.06	-0.02	-0.14	-0.06
Shareholders' equity per share, EUR	1.33	1.30	1.28	1.15	1.08

Turnovers and Price of Shares

Year	Turnover EUR	Turnover Pieces	Average Price EUR	Lowest Price EUR	Highest Price EUR	Closing Price EUR	Market Capitalization EUR[12]
1999	5 624 694.27	1 240 212	4.54	3.75	6.00	4.13	50 652 538
2000	27 106 757.46	3 646 849	7.43	4.20	13.50	6.20	78 388 937
2001	4 863 535.92	908 660	5.35	3.00	7.20	4.28	54 113 654
2002	3 017 824.28	1 178 003	2.56	1.40	4.40	1.41	18 242 054
2003	2 382 013.55	1 287 467	1.85	1.22	3.30	2.50	32 344 068

Financial Information of Biohit in 2004

- Financial statements for 2003: Wednesday, March 31
- Annual General Meeting: Thursday, April 15 at 17:00
- Interim Report 1-3/2004: Friday, May 7 at 10:00 Finnish time
- Interim Report 1-6/2004: Friday, August 6 at 10:00 Finnish time
- Interim Report 1-9/2004: Friday, November 5 at 10:00 Finnish time

12 Market price for capital stock assuming that the market price of the A-share is the same as that of the B-share.

LETTER FROM THE PRESIDENT

Osmo Suovaniemi, President & CEO

In 2003 the net sales of the Biohit Group totalled MEUR 26.3 exceeding the net sales of the previous year by 3.6%. However, the net sales of the last quarter in 2003 was approximately 20% higher than that of the corresponding period in 2002. This growth was due to the success of Biohit's liquid handling products in France and the U.S. The net sales of the Biohit Group continued to be generated primarily by the sales of liquid handling products and service.

The loss of MEUR 0.7 for 2003 resulted from the following items: Depreciations (MEUR 1.6), goodwill amortization (MEUR 0.4), net financial expenses (MEUR 0.2), taxes (MEUR 0,2) and long term R&D expenses (MEUR 1.45). The result of the financial year was affected by the items related with the divestment of the Italian subsidiary Biohit s.r.l. (approximately MEUR 0.5) as well as the unfavorable development of the USD. Moreover, the result of the Biohit Group was affected by the fixed costs related with the business area of diagnostics, which can be considered as an investment in the future development of business.

The cash flow was MEUR 0.9 positive and the equity ratio was 64.7%. The gross investments in 2003 totalled MEUR 1.2.

In the business area of diagnostics Biohit continued to make preparations for the launch of the diagnostic product range. The emphasis of marketing efforts was placed on international evaluations, exhibitions, import licences and the education of distributors. As this work has been more time-consuming than anticipated the sales of diagnostics was only a couple of percents of the overall group sales in 2003. The diagnostic products will be sold through various marketing channels on the international level.

The most efficient and rapid means to adopt the use of the diagnostic products for the benefit of doctors, patients and medicine in general is to seek co-operation with large, internationally operating diagnostic companies. Such collaboration parties might be companies for which Biohit already has, on the basis of its innovations and technologies, manufactured liquid handling products to complement their diagnostic test systems.

In 2004 the main target for Biohit is to benefit from the market potential for the products as well as to increase the level of efficiency and productivity.

Liquid Handling Products for Various Market Segments

The liquid handling products, i.e., pipettors, and their disposable tip are used, e.g., in research, medical and industrial laboratories for the precise and accurate measurement, and analysis of liquid samples and reagents. The liquid handling products offered by Biohit have served as an example for other companies especially with regard to accuracy, reliability and ergonomics. All these factors contribute to the safety of the patient and safety at work. The importance of the said factors is essential for the prevention of work-related upper limb disorders and the improvement of the quality of work[13,14].

In 2003 Biohit increased the number of the market segments for pipettors. The market segments are differentiated in terms of area of use, performance and price. Biohit complemented its electronic eLINE pipettor range with the multichannel models.

The eLINE-range, together with the new mechanical mLINE-range, can be considered as global industrial standards. These most recent products developed and manufactured by Biohit have been designed to enchance especially safety at work. Today laboratories pay much attention to safety due to, e.g., questions related with responsibility.

The global market potential for pipettors and disposable tips is approximately MEUR 550. This market potential may during the following years become threefold, e.g., as a result of the innovations and technologies developed by Biohit. The OEM[15]-customers of Biohit serve as one of the key factors for this market development.

In 2003 Biohit concluded new OEM-agreements with Hamilton, Tyco Healthcare abd Fisher Scientific in the U.S. Biohit renewed its former OEM-agreement with 3M, and concluded a third OEM-agreement with the Johnson & Johnson Group. On the basis of these agreements Biohit will deliver different types of pipettors and tips, which will complement the diagnostic analyzing systems of the said companies. In 2003 Biohit commenced deliveries of electronic pipettors to its competitor, the German company Eppendorf.

13 Mannonen S., Tiusanen T.. Suovaniemi O. (2000). Major Sources of Error of Air Displacement Pipettors. *Internationa Labmate*, April.
14 Mannonen S., Syrjä K. (2000). Safety in Pipetting. *International Labmate*, February.
15 Original Equipment Manufacturer (OEM).
16 Somatic cell hybrid formed by a fusion of cells.
17 Researchers Milstein and Köhler were awarded the Nobel prize in 1984 for the discovery of monoclonal antibodies.
18 The U.S. patent of Biohit 5,308,584: *Cuvette Matrix Tray*.

Diagnostic Tests

The serum-based diagnostic tests, i.e., GastroPanel as well as tests for diagnosing systemic lupus erythematosus (SLE) and celiac disease, are applicable both for research and clinical use. The quick tests for lactose intolerance and the determination of *Helicobacter pylori* -infection are performed in connection with gastroscopy. Biohit is able to provide hybridomas[16] for the production of 30 monoclonal antibodies[17] primarily for research purposes and for diagnosing different types of cancer. The monoclonal antibodies, the number of which have been increased in 2003, serve as key components for the GastroPanel. The cellular fibronectin (cFn) -test kit is intended primarily for research use for studying, e.g., gastric and colon cancers.

In 2003 Biohit finished the development work of the quick tests for lactose intolerance and *Helicobacter pylori*. These tests will be launched in early 2004. The lactose intolerance test has been patented in Finland and in other European countries. The preliminary market feedback has been promising as approx. 17% of the adult population in Finland, and in some countries even as many as 90%, suffer from lactose intolerance, i.e., the deficiency or lack of the lactase enzyme in the small intestine. Moreover, thus far a fast and reliable method for the detection of lactose intolerance has not been available. The lactose intolerance test patented by Biohit may become a part of all gastroscopies, the number of which totals 100,000 annually in Finland. In addition, since the quick test for the determination of *H. pylori* -infection from a biopsy sample is easy and rapid to perform (1-2 minutes) it may also become a part of the tests made in connection with gastroscopy.

The improvements made to the four tests of the GastroPanel examination have increased the co-operation possibilities with large diagnostic companies and service laboratories. An important scientific finding was made in 2003. GastroPanel enables to determine the risk of oesophageal reflux disease and its complication, Barrett´s oesophagus. Barrett´s oesophagus may, on its part, be a risk factor for oesophageal cancer. The prevalence of reflux disease is approximately 25% in the global population.

In 2003 Professor Francesco DiMario, a specialist having consulted AstraZeneca, completed the following booklet: “Non-Invasive Diagnosis for Gastric Diseases”. The booklet provides information on the benefits of the GastroPanel. The publication was distributed by AstraZeneca, a company manufacturing medication for the reflux disease and *H. pylori* -infection, in Italian as: “Un Approccio Non Invasivo Alla Diagnosi Delle Malattie Dello Stomaco” for approximately 34,000 general practitioners in early 2004. Prof. DiMario leads a research project, in which the general practitioner is instructed to use the GastroPanel before treating a patient suffering from stomach pain and discomfort with medication.

GastroPanel and the GastroSoft program, which interprets the results of the GastroPanel, serve as an aid especially for general practitioners for diagnosing gastric symptoms more accurately and commencing targeted treatment (evidence-based medicine). GastroPanel as a method is more sensitive than gastroscopy for detecting changes in the severity of atrophic gastritis. Rapidly available decentralized laboratory diagnostics (GastroPanel and GastroSoft) promote correct diagnosis and targeted treatment reducing, thus, time and costs both for the patient and the health care system.

Analyzing Systems

The liquid handling and diagnostic products as well as instruments form complete systems for different research and clinical purposes. In the business area of diagnostics Biohit focuses on the screening, prevention and determination of gastrointestinal diseases.

In order to develop decentralized laboratory diagnostics Biohit has complemented its products range with microplate instruments manufactured by the U.S. company Bio-Tek. In 2003 Biohit developed in co-operation with another company microplate instruments, which are suitable for a different market segment. The said instruments are based on the use of microplates[18] and the principle of vertical measurement[19].

GastroPanel, and the SLE- and cFN-tests are founded on safe and specific, microplate-based EIA-technology. The said tests can be considered to have become global industrial standards for research, diagnostics and laboratory work as a result of the development of the vertical measurement principle[18,19,20].

The immunoassays such as the GastroPanel, SLE- and cFN-tests can be measured with microplate instruments[18,19]. The number of instruments sold by different companies can be estimated to be approx, hundreds of thousands globally. Biohit aims also to seek co-operation partners in order to offer the GastroPanel as an element for the automated analyzing systems of large diagnostic companies and for systems which are based on other technologies. Biohit is also capable of offering the GastroPanel for other types of analyzing systems. Moreover, Biohit is currently engaged in a project, the purpose of which is to develop an automated analyzing system for the GastroPanel and for the performance of other immunoassays. The purpose of this project, which aims to enhance decentralized laboratory diagnostics, is to promote the sales of the diagnostic tests for the screening, prevention and diagnosis of diseases. The diagnostic tests developed and manufactured by Biohit aim to promote targeted treatment (evidence-based medicine) of diseases related especially with the gastrointestinal tract.

19 Suovaniemi O. (1994). *Automated Instrumen-tation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors*, Ph.D. Dissertation, University of Helsinki.

20 Inventions made by Prof. Suovaniemi in the late 1960s and early 1970s: Adjustable single- and multichannel pipettor (Finnpipette), and the principle of vertical measurement together with its applications (e.g. Multiskan). Finnpipette and Multiskan are trademarks registered by Labsystems Oy. The electronic pipettors developed by Biohit are used by companies such as Becton Dickinson, bioMérieux, Eppendorf, Johnson & Johnson and 3M.

Production Capacity

In 2003 Biohit continued the automatization of the production plant for liquid handling products in Kajaani, Finland, which was taken into use 2000. The Kajaani plant engages in the injection molding of pipettor tips and their parts as well as the assembly of pipettors. Several product lines of the injection molding department have been converted into sterilized, robotically managed and quality-controlled units. The development work has enhanced further the flexibility and quality of production.

The production plant located in Helsinki manufactures injection molding tools which enable the production of pipettor components and other plastic parts. In addition, the Helsinki plant serves as a pilot plant before commencing large scale manufacturing at the main production plant in Kajaani. The premises enable to quadruple the manufacture of pipettors.

The clean room unit, which was taken into use in Helsinki in 2001, enables the pilot and mass production of diagnostic tests. The production capacity totals approximately 60,000 test kits annually. Premises exist for increasing the production capacity. Thus, the capacity does not form a barrier for benefiting from the market potential and the estimated significant growth of net sales.

Market Potential

The liquid handling products and related innovations and technologies can potentially increase considerably the global market share of Biohit. Growth is expected to be generated especially by the new electronic eLINE and the mechanical mLINE pipettor ranges. Biohit aims to increase co-operation with multinational companies in order to enter and penetrate such market segments which would otherwise remain closed.

The following percentages concerning the prevalence of certain diseases exemplify the market potential for the diagnostic tests of Biohit, which have been patented in various countries. In Finland 17% of the adult population suffer from lactose intolerance. In certain countries the incidence may be as high as 90%. The areas of use of the GastroPanel are summarized as follows.

1. Examination of the causes of dyspepsia. Approx. 30% of the global population suffer from dyspepsia at some stage of their lives.
1.1 Over half of the dyspeptic cases are functional. In these cases, the results of the GastroPanel and gastroscopy indicate that the mucosa of the stomach is healthy and functions normally, i.e., no *Helicobacter pylori* -infection, no atrophic gastritis. The GastroPanel distinguishes between functional dyspeptic cases and those caused by atrophic gastritis, which may be symptomless or produce very few symptoms. If the patient suffers from atrophic gastritis it is necessary to perform gastroscopy.
1.2 In the case of organic dyspepsia the findings of the GastroPanel examination is nearly always pathological (atrophic gastritis in the corpus, antrum or both). Gastric cancer, and peptic ulcer are diseases related with organic dyspepsia.

2. GastroPanel provides a diagnosis of *Helicobacter pylori* -infection and atrophic gastritis as well as risk assessment of gastric cancer and peptic ulcer. The prevalence of *Helicobacter pylori* -infection is over 50% of the global population. Of these patients approx. 50% will develop atrophic gastritis at some stage during their lifetime. The prevalence of gastric cancer is 0.1-1.0% and that of peptic ulcer over 10% in the global population.
3. GastroPanel enables to diagnose corpus atrophy, which may cause a deficiency of vitamin B12. The deficiency may increase the risk of dementia, depression and polyneuropathies. The deficiency of vitamin B12 is one factor which increases the level of homocysteine in blood and tissues, which is an independent risk factor for atherosclerosis, and heart and brain strokes. In Finland even as many as 10% of those over 65 years of age may suffer from the deficiency of vitamin B12.
4. GastroPanel enables the assessment of the risk of gastroesophageal reflux disease and its complication, Barrett's oesophagus. The prevalence of gastroesophageal reflux disease is approx. 25% in the global population.

Biohit faces the challenge of actively benefiting from the market potential of the products innovated and developed. This can be achieved by utilizing current sales channels and by entering into collaboration with diagnostic companies operating internationally.

If Biohit succeeds in benefiting from the market potential of its products and in improving the efficiency of its operations it can be anticipated that both the rate of growth and profitability will increase.

I wish to express my sincere gratitude to the personnel of Biohit both in Finland and abroad, to all our shareholders and interest groups for your co-operation and the trust you have demonstrated towards Biohit. I believe that we have been able to create a motivating and a strong basis which serves as a means for the further enhancement of research, medicine and human well-being.

Helsinki, March 15, 2004

Yours sincerely,

Osmo Suovaniemi, M.D., Ph.D.
Professor
President and CEO of the Biohit Group

BIOHIT GROUP

Intellectual Capital as the Key Competitive Factor

Biohit's present management and certain key persons commercialized successfully in the 1970s two inventions made by professor Osmo Suovaniemi. The inventions, which have served as examples for numerous companies worldwide, were the single- and multichannel, adjustable, mechanical pipettes (Finnpipettes[21]) and vertical light path photometry together with its instrument applications (e.g. Multiskan[22]) for research use and immunodiagnostics.

These inventions have been utilized so extensively that they can justifiably be called global industrial standards. The liquid handling instruments and systems based on these inventions served as the foundation for the global business and growth for Labsystems and joint venture Eflab, the companies founded by Suovaniemi in the 1970s, as well as for numerous other companies. It has been estimated that the business generated by the said inventions totals over USD 2.0 billion annually. In a publication by the National Technology Agency of Finland these innovations by Suovaniemi have been assessed as follows: "The multichannel pipetting system and the vertical photometer capable of reading 96-well microtitre plates are Finnish innovations that revolutionised laboratory routines worldwide in the 1970s and 1980s."[23]

The aforementioned annual business totalling over USD 2.0 billion consists of different types of products used, e.g., in research and immunodiagnostics. Currently the markets for products used in PCR-[24] and HTS[25]-applications are growing especially fast. The Nobel prize winning production method of monoclonal antibodies[26] and the PCR-technique[27] utilize applications related with multichannel liquid handling devices and the vertical measurement principle.

The development of enzyme immunoassay methods for research and, in specific, for the diagnosis of cancer and infectious diseases has resulted in the growth of the overall size of the markets to USD billions. It has been estimated that the value of the sales of services related with immunodiagnostics by service laboratories in the U.S., Japan and Europe exceeds USD 40 billion annually.

Biohit focuses solely on those business areas in which it possesses in-depth knowledge on customers needs and international markets, a solid multidisciplinary scientific base, technological expertise and inventions protected by patents[28,29]. The management and key personnel of Biohit have a 10 – 30 years' experience in the R & D, manufacture and international marketing of liquid handling and immunodiagnostic products, instruments and analyzing systems composed of these product groups. The experience, skills and accumulated intellectual assets of the personnel are Biohit's most crucial resources.

Research and Development

Since its foundation in 1988 Biohit has established itself on the global market with its innovative, high technology liquid handling products. During the past decade Biohit has invested in R & D, launched numerous new products, invested in production technologies, automation and quality control, and established an extensive international sales and marketing network. Personnel resources have been strengthened and diversified

The business idea of Biohit is to develop, manufacture and market liquid handling products, diagnostic tests, instruments as well as analyzing systems composed of these product groups.

21 Finnpipette is a registered trademark of Labsystems Oy.
22 Multiskan is a registered trademark of Labsystems Oy.
23 The National Technology Agency of Finland (2001). *Paving the Way for Evidence-Based Medicine: Diagnostics 2000.*
24 The Polymerase Chain Reaction (PCR) technique is used for the amplification of small amounts of DNA.
25 High Through-Put Screening (HTS) refers to the study of large amounts of samples.
26 Milstein and Köhler received the Nobel prize for inventing monoclonal antibodies in 1984.
27 The PCR-technique was invented in 1983 by Kary Mullis, who received the Nobel prize for it in 1993.
28 In January 2000 Biohit, as the first biotechnology company listed on the NM-list of the Helsinki Exchanges. At that time Biohit possessed 16 Finnish patents and 31 patent applications. At that time twenty other companies having recently listed possessed altogether 11 patents and 24 patent applications (Board of Patents and Registration, Taloussanomat January 26, 2000). By the end of December 2003 Biohit possessed 28 Finnish patents and 9 patent applications.
29 *Yksityislääkäri* (2003). Aggressive Innovation and Patenting Strategy: A Route to Success (in Finnish). No 1: 96-98.

The research and development work of Biohit combines the expertise of various fields into integrated knowledge.

through col-laboration with leading researchers at universities and research institutions. The commitment and entrepreneurship of the personnel, members of the board and scientific advisors have been strengthened through ownership of shares and the option program targeted to the entire personnel.

In the early 1990s Biohit focused on liquid handling products and, in addition, continued to develop diagnostic tests and laboratory instruments for new business areas. As of 1999 Biohit's business idea has been to focus on the development, production and marketing of liquid handling products, immunodiagnostics and laboratory instruments as well as on analyzing systems composed of these three product lines.

Biohit's research and development combines expertise in various fields into integrated know-how. The key personnel are experts in the fields of biotechnology, chemistry, electronics, medicine, mechanics, molecular biology, optics, physics, and precision injection molding technology. Biohit's personnel together with scientific advisors representing various academic communities apply in the innovation work, basic and applied research, and R&D knowledge of these areas and different related high technologies.

This multidisciplinary approach, innovations and application of different technologies has produced valuable results for the advancement of research and health care all over the world. A further strength of Biohit's multidisciplinary R & D is the ability to react quickly to new customer needs and product ideas.

Patent Policy

Biohit possesses numerous patents, and its key personnel and management have a 10 – 30 years' experience in the R & D, manufacture and international marketing of liquid handling and diagnostic products, instruments and analyzing systems composed of these product groups. The experience of Biohit's President and CEO, Osmo Suovaniemi, is illustrated, e.g., by the fact that he has been awarded most patents in Finland[30,31], and a few hundred abroad in the fields of medical diagnostics, optics and mechanics.

The comprehensive patent protection in Finland and abroad, which has resulted from Biohit's aggressive patenting policy has formed a solid and reliable basis for Biohit's growth and co-operation with other companies on the global level. Biohit's patents, the high quality of products and accurate deliveries have resulted in the continuation of long-term co-operation with companies such as Beckman Coulter, Becton Dickinson, bioMérieux, Johnson & Johnson and 3M. For the same reason the business of the seven subsidiary companies of Biohit have continued to develop favorably. Also the distribution network comprised of nearly 100 distributors has continued to invest in the sales and marketing of the products of Biohit. Biohit will continue to pay special attention to the development and protection of its multidisciplinary immaterial assets also in the future.

The basis of Biohit's mission is an aggressive innovation and patenting strategy. In pursuing this Biohit's management and numerous key persons have acted as pioneers and examples for many small and large companies as of the 1970s[32]. This foundation guarantees that Biohit is able to develop such products which promote efficient and safe laboratory practices as well as decentralized laboratory diagnostics and related targeted treatment (evidence-based medicine).

Production

The liquid handling products and disposable pipettor tips are manufactured according to the ISO 9001 and ISO 14001 -quality system standards in the Kajaani and Helsinki plants. The main production plant is located in Kajaani whereas the Helsinki production unit serves as a pilot plant.

Biohit's new facilities for the assembly of liquid handling products and injection molding of plastic parts were taken into use in Kajaani in 2000. The injection molding department produces precision molded plastic components, pipettor parts and disposable pipettor tips. Investments were made especially in the automation of injection molding, materials handling and production. The new premises enable to quadruple the current production volume of liquid handling products and plastics.

In the beginning of 2001 Biohit took into use a clean room unit for the production of diagnostic test kits in Helsinki. The premises enables the production of 60,000 test kits annually, and it is possible to quadruple the amount of test kits manufactured.

30 Tekniikka ja Talous *(Technology and Economy)* 8.2.2001: 11
31 Keksintöuutiset *(Innovation News)*. (2001). 4-5: 7.
32 *Yksityislääkäri* (2003). Aggressive Innovation and Patenting Strategy: A Route to Success (in Finnish): No. 1: pp 96-98.

The production facilities of Biohit in Kajaani enable to quadruple the current production volume of liquid handling products and accessories.

Despite of heavy investments made one of Biohit's strengths is that production has not been externalized. As a result, Biohit is able to control the utilization of its production technologies, costs and quality. Biohit, nevertheless, co-operates with certain reliable subcontractors both in Finland and abroad.

International Sales and Marketing

The customer base of Biohit consists of leading laboratories of research institutes, universities, those of medical and biotechnology companies and hospitals. Moreover, the food industry and environmental control laboratories are important customers for Biohit. In addition, Biohit manufactures OEM -products on the basis of its technology and know-how for numerous customers globally.

The international co-operation and customer service network for Biohit's liquid handling products, diagnostics, instruments and systems consists of:

- Subsidiary companies in China (representative office), France, Germany, Japan, Russia, the U.K. and the U.S. The companies are located on Biohit's most important market areas. The companies act as sales and marketing units for Biohit's products and also offer maintenance, calibration and training services. In addition to Biohit products, the units engage in the sales of OEM- and private label -products developed and manufactured by Biohit.
- The 60 main distributors, together with their local distributors form a network of 450 members covering 70 countries.
- Global distribution networks of the most important OEM- and private label -customers.

Quality and Process Development

Biohit operates in a business area in which the strict reliability of the products and the continuation of activities is crucial. Today, the products manufactured for the

Biohit participates annually in numerous exhibitions related with laboratory technology and medicine. Biohit at European Helicobacter Study Group, XVIth International Workshop in Stockholm 3.-6.9.2003. From the left to right in the picture: Professor Kurt Borch, Professor Pentti Sipponen, Biochemist Maria Myllyniemi, Export Manager Outi Vilamo, Director of R&D and Production for Diagnostics Erik Forsblom, R&D Manager for Diagnostics Auli Linnala, Development Manager for Diagnostics Lea Paloheimo.

needs of laboratories must be of high quality, safe and friedly to the user. In addition to product safety, the product must be environmentally friendly over its total lifecycle. Major part of the materials used in the products manufactured by Biohit are recyclable.

One of the new challenges in the future will be the traceability of the performance of liquid handling products. This trend can be seen already via the increased demand of written calibration certificates. The importance of liquid handling products in the control of analyzing processes carried out in laboratories has steadily increased.

In the business area of diagnostics the traceability of the manufacturing process and end products is an absolute necessity.

In 2003 Biohit launched a project, the purpose of which is the development of business and operations. One of the further main goals is to unify the logistics processes of the Biohit Group.

The quality management systems of Biohit are certified according to the following international standards:

- ISO 9001:2000: Quality Management System
- ISO 13485:1996: Quality Management System, IVD / Medical Devices
- ISO 14001:1996: Environmental Quality Management System
- ISO 17025:2000: General requirements for the competence of testing and calibration laboratories.

LIQUID HANDLING

The liquid handling product range developed and manufactured by Biohit encompasses electronic and mechanical pipettors, their disposable tips and maintenance, calibration and training services. The liquid handling product range manufactured by Biohit is the widest in the world today.

Currently, Biohit is the global market leader of electronic pipettors holding an approx. 60% of the world markets. Biohit is also the leading manufacturer of electronic OEM-pipettors in the world. Biohit's OEM-customers include, e.g., Becton Dickinson, bioMérieux, Johnson & Johnson and 3M. As to mechanical liquid handling products, Biohit possesses an approx. 8% share of the world markets, and in the area of disposables slighty under 2%. During the past couple of years the maintenance of liquid handling products has become a new, fastly growing and profitable business area. Biohit's liquid handling products comply with international quality standards and are GS[33]- and CE[34]-qualified.

Biohit's current patents and patent applications feature various innovations, which together with the technologies developed and employed by Biohit, and which have been tested by various multinational companies, enable to offer many new products for different market segments. The current and new market seg-

33 Geprüft Sicherheit (GS): A German product safety standard.
34 Les Communautés Européennes (CE) -marking is a guarantee for authorities, importers and sellers that the product fulfils the requirements set by the European Union.

In 2003 Biohit began the sales of the mLINE pipettor. In the development work of the pipettor special emphasis has been placed on the ergonomical aspects of the liquid handling device. The forces needed for pipetting and tip disposal are small which contributes to reducing the risk of work-related upper limb disorders (WRULDs). The picture displays also the new environmentally friendly refill tip box system.

Biohit is the leading manufacturer of electronic liquid handling devices in the world. The structure, ergonomical design and light weight of Biohit's electronic pipettors take much of the strain out of pipetting and, thus, reduce significantly and help to prevent the development of work-related upper limb disorders. Moreover, the microprocessor-controlled electronic pipettors contribute to minimizing humand error and, thus, improve the accuracy and precision of liquid handling. The picture displays the new generation eLINE -product range which was developed for most demanding liquid handling applications. The eLINE received an honorary mention in the Pro Finnish Design 2001 -competition arranged by Design Forum Finland.

ments vary in terms of the area of application, performance and price.

The value of the market for Biohit's current range of liquid handling products and disposable tips totals USD 500 million annually. This consists of the sales of over 1 million mechanical pipettors, approx. 50,000 electronic pipettors and over 10 billion disposable tips each year. It can be expected that the increasing number of electronic liquid handling applications to be integrated into automated laboratory instruments and analyzing systems, as well as the tightening safety, quality control and efficiency requirements, will considerably reinforce the demand for electronic liquid handling devices in the future.

Electronic Liquid Handling

Biohit's electronic liquid handling products combine electronics, optics, fine mechanics and material technology in a way which simplifies and renders liquid handling more efficient and ergonomical. The microprocessor-controlled electronic pipettors contribute to minimizing human error when pipetting and improve the accuracy and precision of liquid handling.

Biohit's electronic pipettors are available in single- and multichannel configurations and cover the volume ranges of 0.2 µl[35] to 100 ml. They have opened up new dimensions in liquid handling technology in terms of precision, ergonomics and functionality. The ergonomical design and light weight of the electronic pipettors take much of the strain out of pipetting and, thus, help to prevent fatigue and the development of work-related upper limb disorders (WRULDs). For example, the effort required for one pipetting action with a mechanical pipettor may even be equivalent to moving a load of several kilograms with the thumb, whereas using an electronic pipettor requires only 2% of this effort.[36,37,38,39,40,41] According to Hoskins et al. the Occu-

35 1 µl = one millionth part of a liter.

36 Suovaniemi O. (1994). *Automated Instrumentation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors*, Ph.D. Thesis, University of Helsinki.

pational Safety and Health Administration (OSHA) in the U.S. has determined that Repetitive Strain Injuries (RSIs) are the largest single category of injury in the workplace[42].

In order to improve further the safety of pipetting, most of Biohit's electronic pipettors are equipped with filters which protect the internal components of the pipettor from contamination and, as a result, the sample from carryover, e.g., in genetic studies[43,44]. In addition to providing enhanced ergonomics and safety, the electronic pipettor is, as a result of the microprocessor controls, an extremely versatile tool for numerous tasks; one unit can perform pipetting, multiple dispensing and diluting, and the electronic pipettor can also be used for mixing liquid samples.

As a result of the market segmentation made on the basis of different customer needs and price sensitivity Biohit's electronic pipettors can be divided into the following product groups:

- eLINE®: The new generation electronic pipettor range for most demanding liquid handling applications. The ergonomical design of the eLINE and the unique electronic tip ejector reduce considerably the risk for work-related disorders.
- Biohit Proline®: Biohit's basic range of electronic pipettors.
- ePET®: The most cost effective range of Biohit's electronic pipettors which serve as a more ergonomical alternative to mechanical pipettors.
- rLINe: Electronic liquid handling module for robotic applications.

and the following products for large volumes:

- ViscoPet: Electronic pipettor developed especially for the precise and accurate handling of viscous liquids. The device together with Viscotip capillaries makes the ViscoPet particularly suitable for the needs of laboratories processing food and dairy products.
- XL: Pipetting controller and electronic pipettor for the volume range 0.1-25 ml.
- Midi Plus: Pipetting controller for the volume range 1-100 ml.

37 Björkstén M.G., Almby B., Jansson E.S. (1994). Hand and Shoulder Ailments among Laboratory Technicians Using Modern Plunger-Operated Pipettes. *Applied Ergonomics* 25: 88-94.
38 Fredriksson K. (1995). Laboratory Work with Automatic Pipettes: A Study on How Pipetting Affects the Thumb, *Ergonomics* 38 (5): 1067-1073.
39 McGlothlin J.D., Hales T.R. (1995). *NIOSH* (National Institute of Occupational Safety and Health) *Health Hazard Evaluation Report*.
40 Hodgson E. (1996). Work Related Upper Limb Disorders and the Laboratory. *World Directory of Environmental Testing, Monitoring and Treatment.*
41 David G., Buckle P. (1997). A Questionnaire Survey of the Ergonomic Problems Associated with Pipettes and Their Usage with Specific Reference to Work-Related Upper Limb Disorders. *Applied Ergonomics*, Vol. 28, No. 4: 257-262.
42 Hoskins D.B., Erickson J. (1998). Laboratory Ergonomics, the Wake-Up Call: A Case Study on How One Company Relieved Stress and Strain on Its Employees, *Chemical Health and Safety*, January/February.
43 Kolari M., Mannonen S., Takala T., Saris P., Suovaniemi O., Salkinoja-Salonen M.S. (1999). The Effect of Filters on Aseptic Pipetting Lifetime of Mechanical and Electronic Pipettors and Carryover during Pipetting. *Letters in Applied Microbiology* 29: 123-129.
44 Suovaniemi O. (2000). Finnish patent 104885: *Filter*.
45 Kolari M., Mannonen S., Takala T., Saris P., Suovaniemi O., Salkinoja-Salonen M.S. (1999). The Effect of Filters on Aseptic Pipetting Lifetime of Mechanical and Electronic Pipettors and Carryover during Pipetting. *Letters in Applied Microbiology* 29: 123-129.
46 Suovaniemi O. (2000). Finnish patent 104885: *Filter*.

Biohit has segmented the liquid handling markets on the basis of different customer needs and price sensitivity. In 2003 Biohit launched the multichannel eLINE pipettor, which has been designed in specific for the needs of research laboratories.

Mechanical Liquid Handling

Today, mechanical liquid handling products continue to be some of the most commonly used tools in laboratories, and over million pieces are sold annually. The factors contributing to the popularity of the mechanical pipettors are that laboratory personnel are used to them and their lower price compared with electronic devices.

Biohit's mechanical pipettor range covers fixed and adjustable single- and multichannel models for the 0.1 µl – 5 ml volume range. In its development of mechanical pipettors Biohit has again paid special attention to ergonomical aspects. The light weight and smooth plunger action of the pipettors facilitate liquid handling. Moreover, as is the case with electronic pipettors, most of Biohit's mechanical pipettors are equipped with filters, which improve the quality and safety of pipetting[45,46].

Disposable Tips

The pipettors and injection molded plastic disposable tips manufactured by Biohit form together a reliable system[47,48]. Biohit guarantees the precision and accu-

47 Suovaniemi O. (1994). Automated Instrumentation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors, Ph.D. Thesis, University of Helsinki.
48 Mannonen S., Tiusanen T., Suovaniemi O. (2000). Major Sources of Error of Air Displacement Pipettors. *International Labmate*, April.

The accredited calibration laboratory for liquid handling products reinforces the position of Biohit as one of the leading manufacturers of liquid handling devices in the world.

racy of its pipettors when using tips developed and manufactured by Biohit. Further development of pipettor tips is always an integral part of the R & D work on the pipetting system. To support the safety and quality of pipetting Biohit's range of disposables includes, e.g., filter tips.

Maintenance and Calibration Services

As part of its product and marketing strategies Biohit provides maintenance, calibration and training services through its subsidiary and distributor network. During the past couple of years especially the maintenance of liquid handling products has become a new, fastly growing business area.

Today, due to tightening quality control regulations, the customers for liquid handling products are increasingly using accredited calibration laboratories. The calibration laboratory for Biohit's liquid handling products was accredited by FINAS[49] in 2000.

The accreditation of the calibration for liquid handling products performed in the production plants in Helsinki and Kajaani reinforces Biohit's market position as one of the leading manufacturers of liquid handling devices in the world. Currently, there exist only two accredited calibration laboratories in the world.

As a result of the accreditation Biohit is able to offer its customers worldwide calibration certificates for liquid handling devices, which are based on national and international measurement standards. Moreover, Biohit is able to fulfil the international (ISO 17025) and national traceability requirements set for liquid handling devices. Traceable calibration certificates form already now an important part of the reliable analysis services provided by laboratories.[50] The number of Biohit's accredited calibration laboratory is K041.

Liquid Handling in 2003

In the area of liquid handling Biohit continued to develop new pipettor generations. This development work is based on the liquid handling product strategy of Biohit in which new market segments have been identified and created. These segments differ from each other in terms of the area of application, performance and price.

In its development of liquid handling products Biohit has paid special attention to the safety and ergonomi-

49 The Finnish Accreditation Service (FINAS), a part of the Center for Metrology and Accreditation, is a body operating under the Ministry of Trade and Industry. FINAS is a member of the European Co-operation for Accreditation (EA).

50 Mannonen S., Riikonen S. (2000). Accredited Calibration and Future Demands for Pipettors. *International Biotechnology Laboratory*, April.

cal aspects of pipettors, which contribute, e.g., to reducing the risk of work-related upper limb disorders.

In 2003 Biohit launched the multichannel, electronic eLINE pipettors (8 and 12 -channel versions) for the volume range; 0.2 – 1,200 µl. Thus, the eLINE-range was completed. Previously Biohit had launched the single-channel versions of the eLINE for the volume range 0.2 – 5.000 µl.

The electronic eLINE pipettor range has been developed for most demanding liquid handling applications. The microprocessor control and novel construction enable maximum liquid handling performance providing high accuracy and precision. The ergonomical design of the eLINE together with electronic tip ejection reduce considerably the risk of work-related upper limb disorders.

In the area of mechanical liquid handling products Biohit launched the new mLINE® -product family, which covers the volume range 0.5-5,000 µl. The launched single-channel pipettor is completely autoclavable, and in its development work special attention has been paid to its ergonomical properties.

In 2003 Biohit launched new tip boxes and the Refill System for the tips of liquid handling products. The tip boxes are available both as presterilized or non-sterilized. The Refill System is environmentally friendly as the packaging is totally recyclable.

Biohit took into use new automated production lines for pipettor tips. The clean room -based production method enables, i.e., the manufacture of the aforementioned Refill Systems.

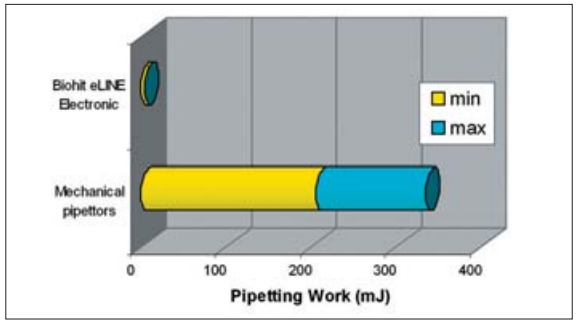
Biohit continued to develop further the maintenance, calibration and training services offered by its subsidiaries and distributors. The calibration laboratories of Biohit S.A. (in France) and Biohit Ltd. (in the United Kingdom) were accredited by COFRAC (Comité Francais d´Accréditation) and UKAS (United Kingdom Accreditation Service), respectively.

In the area of liquid handling Biohit was awarded the following patents:

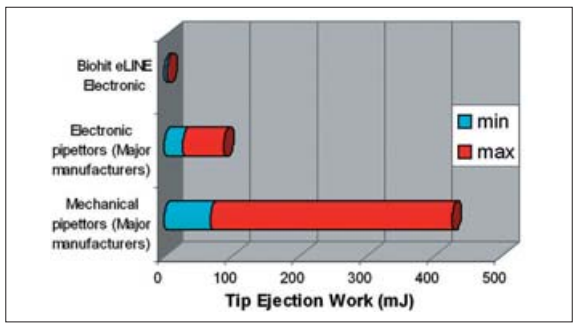
- European patent: 0837731 for the invention “Method for Correcting a Liquid Dispensing Error, and a Liquid Dispensing Device”
- Chinese patent: 99803815.6 for the invention “Suction Device”
- Russian patent 2217235 for the invention “Suction Device”.

In 2003 Biohit published the following articles related with the business area of liquid handling:

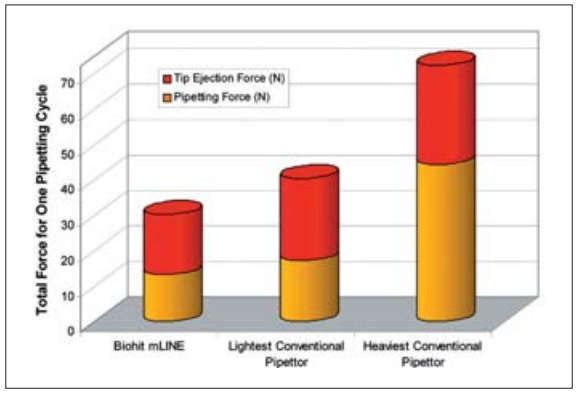
- Mannonen S, Hintikka V, Syrjä K. The Benefits of Electronic Pipetting: How to Choose the Correct Pipettor. *International Labmate Guide* 2002/2003.
- Mannonen S, Nieminen P, Kaasinen J, Andersin K. Raising the Standard of Mechanical Pipetting – The Biohit Solution. *International Labmate* 2003.



Comparison of Pipetting Work for Electronic and Mechanical Pipettors. Biohit electronic pipettors overcome problems related to pipetting ergonomics. The plunger is operated electronically and controlled by a microprocessor, and only a light touch is needed to operate the pipettor. The electronic pipettor reduces the workload and improves the accuracy and precision of pipetting work. In addition, the electronic pipettor reduces the risk of human error and, thus, enhances the quality of pipetting irrespective of the experience of the user.



mLINE Challenges Gravity in Mechanical Pipetting. Biohit's new mechanical pipettor, the mLINE, offers the most novel technology in mechanical pipetting and features light weight for easy handling. As a result of the patented plunger technology, the mLINE requires the lowest pipetting forces of products available on the market. The ergonomical design of the mLINE promotes ease of use.



Comparison of Tip Ejection Work. Tip ejection can be electronically activated, eliminating totally the stress for the thumb, which is unavoidable in mechanical pipetting.

DIAGNOSTICS

Biohit develops, manufactures and markets enzyme immunoassay (EIA) -based test kits and monoclonal antibodies (MAb) primarily for the screening of different types of disease. GastroPanel is a unique test panel for diagnosing *Helicobacter pylori (H. pylori*) -infection and atrophic gastritis as well as for screening the risk of gastric cancer and peptic ulcer, the reflux disease, and its complication, Barrett's oesophagus, from a blood sample. In addition, Biohit offers a serum test for the determination of systemic lupus erythematosus (SLE). In 2003 Biohit finished two new product innovations, i.e., quick tests for diagnosing *H. pylori* -infection and lactose intolerance from biopsy samples.

GastroPanel for Determining *Helicobacter pylori* -Infection and Atrophic Gastritis

Background

Australian doctors, Barry J. Marshall and J. Robin Warren isolated the *Helicobacter pylori* (*H. pylori*) in 1982. This bacterium lives protected from gastric acids on the mucosa of the stomach. *H. pylori* -infection is usually caught in childhood and rarely in adulthood. The infection spreads orally (oral-oral transmission) and via the contents of the stomach (e.g. vomiting) and possibly also via feces. If untreated the infection lasts for a lifetime and causes an inflammation of the stomach, i.e., gastritis. Gastritis is nearly always caused by *H. pylori* -infection. In a small number of cases gastritis may develop as a result of an autoimmune disease. Over half of the global population are infected by *H. pylori* and related gastritis. In half of the infected cases the gastritis develops over the years into atrophic gastritis, which refers to the functional disorder of the mucosa and is caused by inflammation and atrophy of the mucosa of the stomach.

The isolation of the *H. pylori* changed the understanding of the causes of gastric cancer and peptic ulcer. Today it is known that *H. pylori* -infection and gastritis are nearly always related with the development of gastric cancer and peptic ulcer. Before 1982, and even for a long time after that, it was believed that peptic ulcer develops primarily as a result of hypersecretion of acid, stress and anxiety.

Biohit participated in the Digestive Disease Week Symposium in the U.S. in 2002. On the right Professor Barry Marshall, who together with Professor Robin Warren isolated the H. pylori in 1982. On the left Lea Paloheimo, Ph.D., who acts as the Specialist and Development Manager for diagnostics at Biohit.

In reality in 70–90% of the cases the primary cause of peptic ulcer is gastritis or atrophic gastritis caused by *H. pylori* -infection. Other causes are anti-inflammatory analgesics (NSAID drugs) and asperin. In 1994 the International Agency for Research on Cancer (IARC) operating under WHO presented a consensus statement, based on available research results, that gastric cancer is caused by *H. pylori* -infection. *H. pylori* -infection was considered to be related with the development of gastric cancer (carcinogenecity class 1) in a similar way as smoking is related with lung cancer. According to the consensus statement *H. pylori* -infection launches a chain of events, such as the development of atrophic gastritis, which in certain cases leads to gastric cancer.

Gastritis and atrophic gastritis appear in different patients in three different topographical types depending on whether the changes appear in the lower part of the stomach, i.e., the antrum (antrum gastritis), the upper part, i.e., the corpus (corpus gastritis) or both (pangastritis).

The risk for gastric cancer and peptic ulcer is very low when the mucosa of the stomach is healthy and functions normally. The risk of gastric cancer of a patient suffering from atrophic gastritis of the corpus is 5-fold compared to normal population. If both the corpus and antrum are severely atrophic the risk is approx. 90-fold. When only the antrum is severely atrophic the risk of gastric cancer is approx. 20-fold. In addition, the risk of peptic ulcer is approx. 25-fold compared with normal population. It has been estimated that in the U.S. approx. 20 million persons suffer from or develop peptic ulcer during their lifetime[51]. The equivalent number in the Finnish population can be estimated to be approximately 500,000.

GastroPanel enables to screen patients at risk for gastric cancer and peptic ulcer and treat the persons in time. As a method it is as simple as the routine measurement of blood pressure or lipids. The use of GastroPanel promotes, thus, well-being and enbles to decrease health care costs.

Atrophic gastritis and the early stage of gastric cancer are usually symptomless or show only weak symptoms. The surgical removal of an early stage gastric cancer is usually successful. However, the prognosis of a prolonged cancer case showing symptoms is weak; the 5-year survival rate of those surgically treated is only 10-20%[52]. The equivalent survival rate of patients treated early in whom the cancer is restricted to the mucosa and submucosa is approx. 90%. The prevalence of gastric cancer is especially high in certain parts of the world, e.g., in Japan, Asia in general and South America.

Approx. 30% of the global population, i.e., nearly two billion persons, suffer from dyspepsia, the occasional or continuous pain or discomfort in the upper part of the stomach. The only method for examining whether a patient suffering from dyspepsia or *H. pylori*

51 Lim D. (1996). *Microbiology*, 2nd ed.: 522.
52 Wanebo H.J., Kennedy B.J., Chmiel J., Steele G.J., Winchester D., Osteen R. (1993). Cancer of the Stomach. A Patient Care Study by the American College of Surgeons. *Ann. Surg*. 218: 583-592.

-infection suffers from atrophic gastritis has until now been the histological (microscopic) examination of biopsy samples taken in connection with gastroscopy.

The atrophy of the mucosa of the stomach cannot be detected by gastroscopy. The most reliable method for diagnosing atrophy is the histological examination of biopsy samples. However, the said examination does not determine well neither the severity of atrophy nor the malfunctioning of the stomach caused by the damage of the mucosa. The latter condition can be measured by the levels of Pepsinogen I (produced by the corpus), Gastrin-17 (produced by the antrum) and the level of Pepsinogen II (produced by both corpus and antrum). GastroPanel enables to detect very small changes in the production of Pepsinogen I and II and Gastrin-17. A decrease in the said levels indicates that the atrophy is becoming more severe whereas an increase in the levels demonstrate that the atrophy is healing, thus, reducing the risks of related diseases.

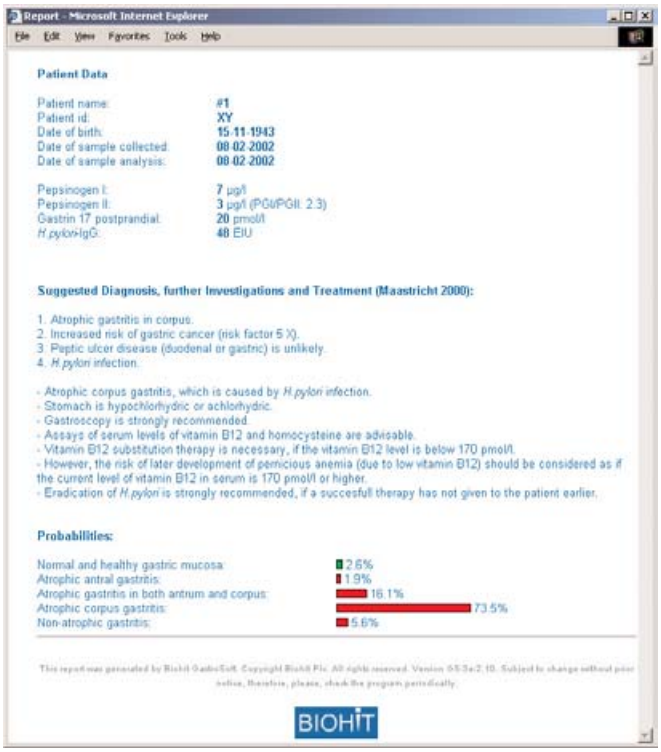
The biopsies taken during gastroscopy represent approx. 1/4000 of the entire area of the mucosa of the stomach. It is fully possible that this small a sample does not reliably reveal atrophic gastritis or *H. pylori*. This might explain why GastroPanel examination and histological analysis of biopsies taken during gastroscopy give the same result only in approx. 80% of cases. For instance, if the biopsy was taken from a severely atrophic part of the mucosa of the stomach, *H. pylori* cannot be found in the biopsy. Studies show that the gastroscopy results obtained by two average-skilled doctor teams are the same in only 50% of cases, and even between two top teams in maximum 80% of cases.

As invasive gastroscopy is often uncomfortable for the patient, expensive and its availability limited, the patient is usually treated only on the basis of anamnesis, symptoms or clinical examination. Many cases have demonstrated the unreliability of an examination made on the basis of symptoms, which often leads to incorrect conclusions.

Severe consequences may result from delays in targeted treatment and further examinations based on a correct diagnosis. Without a correct diagnosis the treatment may be delayed and the disease may become impossible to cure. This, at worst, may increase the risk of deaths, decrease the quality of life, and increase human suffering and health care costs.

H. pylori -infection is diagnosed worldwide by using serological tests, breath tests and antigen tests of the feces. These tests enable to diagnose only whether the patient is infected or not. GastroPanel makes a major contribution to these tests. GastroPanel enables to diagnose *H. pylori* -infection, atrophic gastritis, its severity and location (corpus, antrum or both). The meas-

Test panel developed by Biohit for diagnosing atrophic gastritis and H. pylori -infection, and for screening the risk of gastric cancer and peptic ulcer from blood samples. GastroPanel can replace gastroscopy as the initial method when examining patients suffering from stomach pains, discomfort and possible atrophic gastritis caused by H. pylori -infection.



The increase in the level of the H. pylori -antibody in blood (48 EIU) indicates the presence of H. pylori -infection. Simultaneously, the probability value of corpus gastritis is high (73.5%). It is highly probable that the patient suffers from atrophic corpus gastritis due to H.pylori -infection. In such a case the risk for gastric cancer is estimated to be five fold compared to the normal population. The stomach is hypochlorhydric or achlorhydric. Therefore, the risk of peptic ulcer is low ("no acid, no wound"), if the person is not using NSAID-drugs. The GastroSoft program suggests gastroscopy as well as assays of the serum level of vitamin B12 and homocysteine. Vitamin B12 substitution therapy is necessary if the level of vitamin B12 is under 170 pmol/l. In case the H. pylori -infection has not been previously treated, the eradication of H.pylori is strongly recommended, and the treatment should be confirmed. Eradication of the H. pylori -infection supports the healing of atrophic gastritis as well as reduces the risks of related diseases. Atrophic gastritis is often related with the risk of gastric cancer. The deficiency of vitamin B12 is a risk fator for dementia and polyneuropathies. The deficiency of vitamin B12 is an independent risk factor for atherosclerosis and heart and brain strokes.

urement of the levels of Pepsinogen I, Pepsinogen II and Gastrin-17 enable to assess the status and functioning of the entire mucosa of the stomach.

Diagnosing and Treating Upper Stomach Problems

When treating a patient suffering from upper stomach problems, the safest and most economical "acceptable examination and treatment method" before medication is to try to get information about the status of the mucosa of the stomach (is it healthy and functioning) and the nature of the stomach disease (functional dyspepsia or dyspepsia related to some organic disease). To obtain this information, gastroscopy and the histological examination of biopsy samples has thus far been the only good procedure, which at the same time burdens the patient, and is expensive and time-consuming. As a result of decades of basic Finnish medical research, a new innovation has been developed – GastroPanel. GastroPanel examination is done on a blood sample and it reveals the status and functioning of the mucosa of the stomach. GastroPanel examination usually gives the same results as gastroscopy. However, gastroscopy is a subjective method and dependent on the professional skills of both the endoscopist and the pathologist analyzing the biopsies.

GastroPanel

GastroPanel® examination measures the levels of Pepsinogen I and II, Gastrin-17 and *H. pylori* -antibodies from a patient's blood sample. On the basis of the results of these tests, it is possible to determine whether the patient suffers from gastritis caused by *H. pylori* (inflammation of the mucosa of the stomach), whether the gastritis has become atrophic (loss of glands in the mucosa and serious functional disorder) and in which part of the stomach the changes are located (corpus, antrum or both). Using blood samples, GastroPanel examination makes it possible to find patients with increased risk of stomach cancer or peptic ulcer, and who, therefore, need to be immediately referred to further examinations and treatment.

Pepsinogens and Gastrin-17. The more difficult the atrophic gastritis of the mucosa of the stomach corpus, the lesser the amount of Pepsinogen I and the lesser the relation between Pepsinogen I and II are. Similarly, the lower the level of Gastrin-17 measured in the blood sample, the more severe is atrophic gastritis of the mucosa of the antrum. Thus, levels of the Pepsinogens and Gastrin-17 measured in the blood sample quantitatively describe the status of the entire stomach, its functional condition and the severity of the disorder.

GastroSoft

Based on laboratory values obtained with the GastroPanel examination, the GastroSoft® computer program gives a diagnosis of *H. pylori* -infection and atrophic gastritis and determines risk factors for gastric cancer and peptic ulcer. Also, the program gives a recommendation for the eradication treatment of *H. pylori* based on the Maastricht 2 (2000) consensus guidelines. If needed, the program gives recommendations for gastroscopy and measuring the levels of vitamin B12 and homocysteine. Depending on the symptoms of the patient and the results of the GastroPanel examination, GastroSoft reminds of the risks of gastroesophageal reflux disease and its complication, Barrett's oesophagus.

Furthermore, a new stochastic program gives a percentage of likelihood for different statuses of the mucosa of the stomach: 1) normal and healthy mucosa, 2)

Biohit's GastroPanel-test and the GastroSoft-program interpreting the results can replace gastroscopy (in the picture) as the initial method when examining patients suffering from stomach pains and discomfort, and atrophic gastritis. Gastrosocopy is relatively expensive, disliked by patients and cannot be performed on all occasions due to limited health care resources.

atrophic antrum gastritis, 3) atrophic antrum and corpus gastritis, 4) atrophic corpus gastritis and 5) non-atrophic gastritis. When repeated GastroPanel examinations are carried out for the patient, the doctor can use the changes in the likelihood profile to determine how the status and functioning of the stomach mucosa of the patient is developing.

Helicobacter pylori -Infection. The prevalence of *H. pylori infection* is over 50% of the global population, and it is usually caught already in childhood. *H. pylori* -infection on the mucosa causes gastritis, which refers to inflammation of a normally functioning mucosa. In approx. half of the cases gastritis develops over the years into atrophic gastritis, which refers to inflammation and withering of the mucosa (loss of glands in the mucosa) resulting in a severe functional disorder. Peptic ulcer is almost always at least partially caused by *H. pylori* -infection and atrophic gastritis caused by it, and also sometimes by NSAID dreugs. The majority of abdominal cancer cases are related to *H. pylori* -induced gastritis and atrophic gastritis.

Atrophic gastritis, dyspepsia and reflux disease of the oesophagus. Atrophic gastritis is usually symptomless, and therefore "underdiagnosed". GastroPanel examination is recommended for screening and diagnosing *H. pylori* -infection and atrophic gastritis as well as for determining the severity of dyspepsia (pain or discomfort in the upper part of the stomach) before initiating medication. *H. pylori* tests alone (inhalation test, antigen test of stools, antibody test or studying the biopsy sample) do not indicate whether the muosa of the stomach is atrophied or healthy and functions normally.

Up until now, atrophic gastritis and related disease risks could have only been determined with the histological examination of biopsy samples taken in connection with gastroscopy. Now, atrophic gastritis and its severity and location (in corpus, antrum or both) and the related risks as well as *H. pylori* -infection can be diagnosed reliably and economically with GastroPanel examination done using a blood sample. The GastroSoft program, which analyses GastroPanel data, also indicates the risk of gastroesophageal reflux disease and its severe complication, Barrett's oesophagus. This information is useful when considering proper treatment for the patient.

Atrophic gastritis can be treated. If atrophic gastritis caused by *H. pylori* -infection is diagnosed early enough, it can in most cases be treated with successful eradication therapy of *H. pylori*, thus, probably avoiding gastric cancer and peptic ulcer. Treating atrophic gastritis of the mucosa of the stomach probably also avoids diseases caused by the deficiency of vitamin B12, dementia, depression and peripheral nervous damage. The deficiency of vitamin B12 increases the amount of homocysteine in the body, which is an independent risk factor for atherosclerosis and heart and brain strokes.

When should H.pylori infection be treated?
H. pylori can with certain restrictions be considered as one of the normal bacteria of the gastrointestinal tract, and, thus, it is not always necessary to eradicate it. Approximately 50% of the global population suffer from *H. pylori* -infection. Approx 50% of the persons infected will develop atrophic gastritis. The related risks can be decreased or completely removed with the eradication therapy of *H. pylori*.

If a person under 45 years of age suffers from dyspepsia and *H. pylori* -infection, the current treatment practice recommends eradication of *H. pylori* with antibiotics and PPI[53] ("test-and-treat"). Positive treatment result is obtained in only approx. 10% of cases with respect to alleviating symptoms. Contrary to current practice, *H. pylori* -infection with patients of any age must only be treated if the patient has been diagnosed with atrophic gastritis and/or peptic ulcer.

Expensive and unnecessary eradication treatment of *H. pylori* decreases the quality of life and increases the resistance of bacteria to antibiotics, hypersensitivity to antibiotics and gastroesophageal reflux disease as well as causes imbalance of normal intestinal bacteria flora for at least half a year thus increasing gastrointestinal tract problems, dysfunctions and possibly even the risk of colon and breast cancer[54].

GastroPanel examination is a simple, cheap and safe method for monitoring potential atrophic gastritis development of *H. pylori* -infected patients and related risks every second year or even more rarely. GastroPanel examination is the recommended method (in addition to gastroscopy or instead of it) to monitor the healing of atrophic gastritis after eradication therapy of *H. pylori*. However, GastroPanel records positive or negative changes in atrophic gastritis more precisely than gastroscopy.

Summary of the Indications of the GastroPanel and Its Benefits

1. Separate diagnostics for dyspepsia. One third of the global population suffers from dyspepsia.
1.1 Over half of dyspepsias are functional. In these cases, GastroPanel and gastroscopy biopsy analyses show that the mucosa of the stomach is healthy and functions normally (no *H. pylori* -infection and no atrophic gastritis). GastroPanel examination can be used for screening out functional dyspeptic patients from those who suffer from symptomless or weakly symptomatic atrophic gastritis and who need to undergo gastroscopy.
1.2 In case of dyspepsia related to an organic disease of the stomach, the GastroPanel finding is almost always pathological (atrophic gastritis either in the corpus or antrum of the stomach or in both). Diseases related to organic dyspepsia are, e.g, gastric cancer and peptic ulcer.
2. Diagnostics of *H. pylori* and atrophic gastritis and risk assessment of gastric cancer and peptic ulcer resulting from atrophic gastritis. Over half of global population suffers from *H. pylori* -infection. About half of these people develop atrophic gastritis at some stage of life. GastroPanel examination gives a diagnosis of *H. pylori* -infection and atrophic gastritis and an assessment of risks for gastric cancer and peptic ulcer. The incidence of gastric cancer is 0.1 to 1.0% and the incidence of peptic ulcer disease is over 10% of the global population.
3. Screening and diagnostics of the corpus section of the mucosa of the stomach. Atrophic gastritis of the corpus may cause the deficiency of vitamin B12, which may increase the risk of, e.g., dementia, depression and the damage of the peripheral nervous system. The deficiency of vitamin B12 is one of the reasons for the increase of the level of homocysteine in the body, which is a risk factor for atherosclerosis and heart and brain strokes. Due to corpus atrophy, celiac disease and lack of rich nutrition, up to 10% of over 65 year old patients suffer from the deficiency of vitamin B12 in Finland. Especially vegetarians face a risk of the deficiency of vitamin B12.
4. GastroPanel examination can be used for assessing the risk of oesophageal reflux disease and its complication, Barrett's oesophagus. "Reflux chain": from a healthy stomach to reflux disease, erosive oesophagitis, Barrett's oesophagus and ultimately cancer of the oesophagus. The incidence of the reflux disease is approximately 25% of the global population.
5. Benefits of GastroPanel Examination
- Simple blood sample -based test
- Non-invasive – therefore, risk-free and comfortable for the patient
- Results available quickly – fast to diagnose
- Easy and reliable interpretation of the results with the GastroSoft program
- Promotes selecting and prioritizing of patients for gastroscopy
- Helps in gastroscopy to locate atrophy in corpus, antrum or both
- Promotes screening, examination and treatment of patients at risk for gastric diseases
  – Promotes the prevention of diseases
  – Promotes the follow up of the treatment of gastric cancer
- Reduces trial treatments and related problems and costs
- Promotes evidence-based medicine, i.e., reaching first a correct diagnosis and then commencing targeted treatment
- Reduces healthcare costs
- Improves the level of healthcare and quality of life

In Finland, considerable annual savings in healthcare costs and other costs are possible by using the GastroPanel examination as the primary examination of patients suffering from stomach problems, for certain risk groups and for the early diagnosis of normal patients. GastroPanel examination saves the patient from premature and unnecessary gastroscopical examinations and trial treatment promoting, thus, evidence-based medicine according to the principle of lege artis, which should always be the primary objective in medicine.

Vitamin B12 and Homocysteine

Atrophic gastritis of the corpus, which is caused by *H. pylori* -infection or more rarely by an autoimmune dis-

53 Proton pump inhibitors (PPI) prevent the secretion of acids by mucosal glands.
54 *Journal of American Medical Association* 2004; 291:827-35.
55 Kts. http://www.b12.com.
56 Kts. http://www.homocysteine.com.
57 Ranta P., Helske T., Kääriäinen I., Mäki T., Saarinen P., Kekäläinen L., Suovaniemi O., Härkönen M., Sipponen P. (2001). Serum Pepsinogen I Test Reveals Cases of Vitamin B12 Deficiency without Anemia in Patients with Gastric Corpus Atrophy. Presentation at the EUROMEDLAB 2001 -Congress, Prague, Chech Republic 26.-31.5.

ease results in the malabsorption of vitamin B12. Approximately 10% of patients with atrophic gastritis will suffer from severe atrophic gastritis of the corpus area of the stomach. The risk of the said patients to suffer from diseases related with the deficiency of vitamin B12 is very high. The deficiency of vitamin B12 increases the level of homocysteine in the body. Homocysteine is an intermediate product of metabolism. The increased level of homocysteine in blood and tissues signal a serious disturbance of methionine metabolism in the cells. The deficiency of vitamin B12 is related with dementia, depression, damages of the peripheral nervous system, and increases the risk of these diseases[55]. An elevated level of homocysteine in the body increases the risk of atherosclerosis and heart and brain strokes [56,57,58].

Humans and other mammals gain the necessary vitamin B12 from nutrition. The reason is that only micro-organisms are able to produce the said vitamin. The absorption of vitamin B12 from the small intestine requires a healthy, normally functioning mucosa of the corpus. Those patients suffering from atrophic gastritis need substitute treatment for vitamin B12.

An observation, which needs to be taken seriously, is that the damages of the brain tissue and peripheral nervous system are irreversible and develop already years before the pernicious type of anemia caused by the deficiency of vitamin B12 occurs.

Cellular Fibronectin

In the 1990s Biohit developed a blood test which serves as an indicator of the cancer of the gastrointestinal tract or its early stages. Biohit patented the method in the U.S. in 1995 and in Europe in 1996[59]. The invention enables possibly to trace gastric cancer or the cancer of the large intestine by measuring the level of cellular fibronectin (cFn) in blood[60].

Fibronectins are adhesive glycoproteins that have a role in a variety of cell contact processes, cell differentiation, and oncogenic transformation. When cancer is developing in the gastrointestinal tract the concentration of cellular fibronectin in blood increases in certain cases. As to gastric cancer it has been demonstrated that as the cancer advances the level of cFn increases in blood. The serum-based cFn test is currently in the phase of research and development. In 2003 in total 8,000 patients were examined in China with the GastroPanel and the cFn test. The results of the study are currently under analysis.

Monoclonal Antibodies

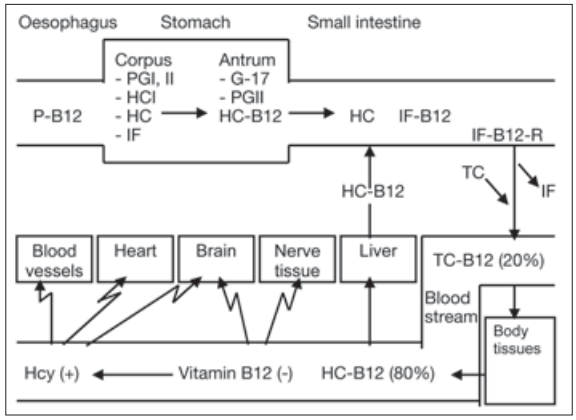
The different test kits of the GastroPanel are based on immunodiagnostics and on the use of Biohit's monoclonal antibodies (MAbs)[61] and microplates[62], which can be used in vertical measurement applications[63].

Biohit manufactures Pepsinogen I, Pepsinogen II and Gastrin-17 -antibodies which are related with the GastroPanel. These have been proven to be highly

58 Härkönen M., Nikulin M, Sande N., Suovaniemi O., Sipponen P. (2001). Atrophic Corpus Gastritis Raises the Serum Levels of Homocysteine. Presentation at the Digestive Disease Week - Congress, Atlanta, U.S.A, 20.-23.5.

59 U.S.-patent 5,420,012 and EP-patent 0399271: *Method for the Detection of Reactive Conditions.*

60 Ylätupa S. (1996). *The Development of a Method for Quantification of Cellular Fibronectin EDAcFn and Its Clinical Applications*, Ph.D. Thesis, University of Helsinki.



Metabolism of Vitamin B12 and Consequences of Its Distortions

The absorption of vitamin B12 from nutrition is distorted when the mucosa of the corpus area of the stomach is atrophic. This results from the fact that the atrophic mucosa of the corpus does not secrete the intrinsic factor (IF) and haptocorrin (HC). In nearly 90% of the cases the atrophy of the mucosa is caused by Helicobacter pylori -infection and in less than 10% of the cases by autoimmune disease. If the atrophy of the mucosa becomes chronic the risk of gastric cancer and peptic ulcer increases. This risk can be determined by measuring from a blood sample the concentration of Pepsinogen I secreted by the mucosa of the corpus and the concentration of Gastrin-17 secreted by the mucosa of the antrum.

Gastric acid and proteolytic enzymes in the stomach release vitamin B12 from the proteins of food. The haptocorrin (HC) of the gastric juice binds the vitamin B12. The protease enzyme secreted by the pancreas breaks down the HC-B12 complex produced, and the vitamin B12 released is bound by the intrinsic factor. The IF-B12 complex is absorbed by the epithelial cells of the small intestine by the receptors of the cell membranes. The vitamin B12, released from the IF-B12 complex, binds with transcobalamin (TC). This results in the TC-B12 complex (holo-transcobalamin). The TC-B12 complex is released into the blood stream and is subsequently recognized and taken up by specific receptors present in all cell types. This complex, which is physiologically active, includes approx. 20% of the total amount of vitamin B12 present in blood. Its concentration decreases rapidly if the absorption of vitamin B12 is distorted. The half-life of the TC-B12 complex in the body is only 0.75 day and that of the HC-B12 complex approx. 9 days. The HC-B12 complex is stored in the liver and kidneys.

Vitamin B12 is solely produced by micro-organisms. Thus, vitamin B12 must be received from nutrition, and if the corpus area of the stomach is atrophic, by injections of vitamin B12. The lack of vitamin B12 in the body is an increasingly growing health problem worldwide and it concerns especially the elderly.

The lack of vitamin B12 leads in less than a year to distortions of the activity of the neural tissues, depression and dementia. These illnesses begin to develop already before the development of noticeable pernicious type of anemia, and they can become irreversible if the diagnosis and treatment are delayed. Moreover, in connection with the lack of vitamin B12, the concentration of homocysteine (Hcy) in tissues and blood increases, which increases the risk of atherosclerosis and thromboembolic diseases.

Biohit's microplate readers and washers are delivered preprogrammed for Biohit's diagnostic tests. The picture displays the BP 800 microplate washer and the Gastrin-17-test kit of the GastroPanel.

specific also for immunohistochemical analyses. This expands the area of use of the said antibodies also to, e.g., pathological laboratories.

Biohit also manufactures and markets 27 other MAbs, which are suited for immunohistochemistry and used in basic research as well as for classifying different types of cancer from tissue samples[64,65,66,67]. These MAbs have been developed specifically for human extracellular matrix components, human integrins, human cytoskeletal polypeptides, human neurotransmitter substances, human spectrins and human endothelial cell surface markers.

Diagnosis of Systemic Lupus Erythematosus

Biohit has developed a novel method for diagnosing systemic lupus erythematosus (SLE). SLE is a prototype of autoimmune diseases, which with its various symptoms resembles rheumatic diseases. The development and technology of the test are based on an international patent acquired exclusively by Biohit[68].

The presence of DNA antibodies in the blood of a patient is typical of SLE. Unlike in the conventional DNA antibody tests, which use purified calf thymus DNA as capture antigens for autoantibodies, the newly developed Biohit anti-telomere antibody assay is based on the use of the double-stranded telomeric DNA as the capture antigen for the binding of SLE antibodies.

Biohit's telomere antibody test measures in a sensitive and specific enzyme immunoassay procedure (EIA) telomere antibodies in the serum of an SLE patient. On the basis of the titers of these antibodies it is possible to distinguish SLE, e.g., from rheumatoid arthritis.[69,70] The observation that telomerase activity is detected in 85% of all cancers has made the telomerase enzyme a new cancer marker and added special interest on telomere research itself[71]. The renowned researcher on rheumatic diseases and SLE, professor D.J. Wallace, together with his research team has published positive results on the SLE-test[72].

The test kit patented by Biohit for determining SLE from a blood sample has been evaluated in Finland. Moreover, there exists evidence that the test kit enables to assess the clinical activity of the SLE[73]. As SLE resembles rheumatic diseases the SLE test can be used among other tests in determining the said diseases. Approximately 2% of the global population suffer from rheumatic diseases and 0.1 - 0.4% from SLE.

61 Researchers Milstein and Köhler were awarded the Nobel prize in 1984 for the discovery of monoclonal antibodies.
62 Biohit's patent U.S. 5,308,584: *Cuvette Matrix Tray* (microplate).
63 Suovaniemi O. (1994). *Automated Instrumentation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors*, Ph.D. Thesis, University of Helsinki.
64 Ylätupa S. (1996). *The Development of a Method for Quantification of Cellular Fibronectin EDAcFn and Its Clinical Applications*, Ph.D. Thesis, University of Helsinki..
65 Linnala A. (1998). *Tenascin, Fibronectin, Laminin and Their Integrin Receptors in Human Cell Cultures*,Ph.D. Thesis, University of Helsinki.
66 Jahkola T., Toivonen T., Nordling S., von Smitten K., Blomqvist C., Virtanen I. (1996). Expression of Tenascin in Invasion Border of Early Breast Cancer Correlates with Higher Risk of Distant Metastasis. *Int. J. Cancer (Pred. Oncol.)* 69: 445-447.
67 Jahkola T., Toivonen T., Nordling S., von Smitten K., Virtanen I. (1998). Expression of Tenascin-C in Intraductal Carcinoma of Human Breast: Relationship to Invasion. *European Journal of Cancer*, Vol. 34, No. 11: 1687-1692.
68 E.g., U.S. patent 5,700,641: *Diagnostic Method, Test Kit, Drug and Therapeutic Treatment for Autoimmune Disease*.
69 Salonen E-M., Ruuskanen L., Friman C. (1996). Anti-Telomere Antibodies in SLE. *Arthr. & Reum*. 39: 40.

Phytoestrogens and the Prevention of Cancer

Biohit's policy is to continue to develop unique diagnostic tests in the fields of cancer detection and prevention. For this purpose Biohit aims to develop in the long range, in collaboration with Professor Herman Adlercreutz, tests for urine and serum phytoestrogens. These tests, which are performed using enzyme immunoassay techniques and monoclonal antibodies, are based on over 20 years of basic research. Biohit currently has monoclonal antibodies for these tests.

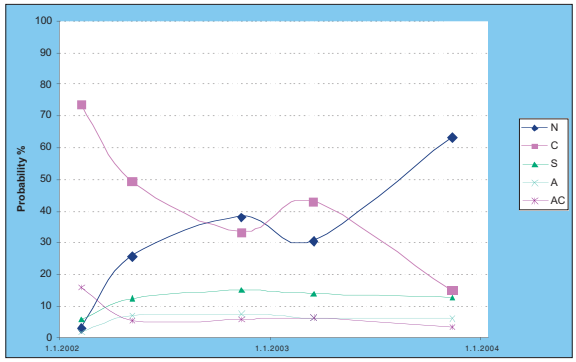
Low concentrations of phytoestrogens may signal a risk for certain forms of cancer, e.g., large bowel, breast and prostate[74,75,76,77], as well as for ischemic heart disease[78]. In such cases the prevention of the diseases involves changes in diet to include more whole grain bread, berries, certain vegetables and soybean products[79,80]. People are more and more interested in nutrition and health. For this reason research work on phytoestrogens is undertaken very intensively worldwide.

Diagnosis of Lactose Intolerance

Over 17% of the adult population in Finland suffer from lactose intolerance. In Asian and African countries there may be as many as 90% of the population suffering from the disease. Lactose intolerance is caused by the deficiency or a very low level of the lactase enzyme, which breaks down milk sugar (lactose), in the surface epithel of the mucosa of the small intestine. The deficiency causes disorders of the stomach, e.g., diarrhea and swelling when consuming milk products. It has not been a long time since lactose intolerance was considered a psychosomatic disease[81].

Patients seeking medical treatment due to undefined stomach disorders are often ordered to a gastroscopy. However, lactose intolerance cannot be diagnosed on the basis of gastroscopy or the microscopic evaluation of biopsy samples. This is due to the fact that the lack of the enzyme does not show on the biopsies and, as a result, the structure of the mucosa seems normal. The lack of the lactase enzyme must be determined biochemically from a biopsy sample in the laboratory or on the basis of a lactose load or breath test. All these tests are time-consuming, strenuous for the patient, expensive and unreliable.

Biohit's quick test for determining lactose intolerance (hypolactasia of the small intestine) is based on the fact that, in connection with gastroscopy, a biopsy taken from the mucosa of the upper part of the small intestine is examined immediately. After 15 minutes the change in the color of the test liquid informs whether the lactase enzyme is present in the biopsy sample or not. Normally the color changes as the lactase enzyme of the sample breaks the lactose, i.e., the milk sugar, in the reagent. If the color remains unchanged or changes slightly, the patient suffers from lactose intolerance (hypolactasia of the small intestine). Biohit's unique POC-test[82,83], enables, when performing gastroscopy, to find quickly those patients who suffer from lactose intolerance. For this reason the quick test should be used in connection with gastroscopy for determining possible lactose intolerance.



Probability of the types of atrophic gastritis (A = Antrum, AC = Antrum and Corpus, C = Corpus, S = non-atrophic gastritis, N = normal and healthy gastric mucosa) before and after treatment, on the basis of classification made by the GastroSoft program (Helipak – K treatment on 20 February 2002). The figure illustrates the decrease in the probability of the corpus atrophy as a function of time. Likewise the probability of the normalized state of the mucosa increases. This is an indication of a healthy mucosa; a condition which is a result of a successful eradication therapy of the H. pylori.

Relative probabilities of the different types of atrophies serve as a means to monitor the status of the stomach after H. pylori eradication therapy.

70 Salonen E-M., Wallace D.J., Metzger A., Morris R., Avaniss-Aghajani E. (1998). Anti-Telomere Antibodies Are Highly Specific for Systemic Lupus Erythematosus (SLE). *Arth. & Reum.* 41: 247.

71 Shay J.W. (1997). Telomerase in Human Development and Cancer. *Journal of Cellular Physiology* 173: 266-270.

72 Wallace D.J., Salonen E-M., Avaniss-Aghajani E, Morris R., Metzger A.L., Pashinian N. (2000). Anti-Telomere Antibodies in Systemic Lupus Erythematosus: A New ELISA Test for Anti-DNA with Potential Pathogenetic Implications. *Nature* 9: 328-332.

73 Salonen E.M., Miettinen A, Valle T.K., Koskenmies S., Kere J., Julkunen H.: Anti-telomere Antibodies in Systemic Lupus Erythematosus (SLE): A Comparison with Five Antinuclear Antibody Assays in 430 Patients with SLE and Other Rheumatic Diseases. *Ann. Rheum. Dis.* Submitted for publication.

74 Adlercreutz H., Fotsis T., Heikkinen R., Dwyer J.T., Woods M., Goldin B.R., Gorbach S.L. (1982). Excretion of the Lignans Enterolactone and Enterodiol and of Equal in Omnivorous and Vegetarian Women and in Women with Breast Cancer. *Lancet* 2: 1295-1299.

75 Adlercreutz H. (1990). Western Diet and Western Diseases: Some Hormonal and Biochemical Mechanisms and Associations. *Scand. J. Clin. Lab. Invest.* 50, Suppl. 201: 3-23.

76 Adlercreutz H., Mazur W. (1997). Phyto-Oestrogens and Western Diseases. *Ann. Med.* 29: 95-120.

77 Adlercreutz H., Mazur W., Kinzel J., van Reijsen M., Bertels P., Elomaa V.-V., Watanabe S., Wähälä K., Mäkelä T., Hase T., Landström M., Bergh A., Damber J.-E., Åman P., Zhang J.-X., Hallmans G. (1997). Phytoestrogens and Prostate Disease. In *Fundamentals of Cancer Prevention* (Ed. Conney A.H., Ito N., Sugimura T., Terada M., Wakabayashi K. and Weinstein I.B.). Princess Takamatsu Cancer Research Fund, Tokyo, pp. 22-24.

78 Adlercreutz H., Mazur W. (1997). Phyto-Oestrogens and Western Diseases. *Ann. Med.* 29: 95-120.

79 Adlercreutz H. , Mazur W. (1997). Phyto-Oestrogens and Western Diseases. *Ann. Med.* 29: 95-120.

80 Griffiths K., Adlercreutz H., Boyle P., Denis L., Nicholson R.I., Morton M.S. (1996). *Nutrition and Cancer*. ISIS Medical Media, Oxford, pp. 1-173.

81 Huttunen J., (2004) Persian Gulf War, Amalgame and Silicon Breasts. A Chemical Poisoning or a Psychosomatic Symptom? *Duodecim 2004*; 120:496-8. (In Finnish)

82 Point-of-Care (POC) -test is performed quickly close to the patient.

83 Sipponen P., Suovaniemi O., Tamminen J. (2000) Finnish patent 106212: *Method for the Determination of Disaccharidases and Kit Therefor.*

Biohit's microplate washer, which may, as a result of featuring a precise micro-stepping syringe pump, be used also as a rapid microplate dispenser.

Instruments

The business idea of Biohit is to offer its customer base complete analyzing systems, which consist of liquid handling products, diagnostic tests, instruments used for the analysis of the results, software as well as maintenance, calibration and training services. In the business area of instruments Biohit supplies products for the following three market segments: instruments used in research, those used in clinical applications, and instruments used in industrial applications.

Biohit's GastroPanel and other test kits as well as the analyzing systems are very well suited for decentralized laboratory diagnostics performed close to the patient by the doctor. Decentralized laboratory diagnostics is a prerequisite for the close interlinkage between the examination and treatment of the patient (evidence-based medicine).

Research and Development of Instruments and Market Potential

Already in the late 1970s the current management of Biohit and key personnel commercialized succesfully two inventions made by Dr. Osmo Suovaniemi at the end of 1960s: the single- and multichannel adjustable mechanical liquid handling devices (Finnpipettes[84]), and vertical photometry and its instrument applications (e.g. Multiskan[85]). Biohit has researched and developed further vertical measurement principles since the end of the 1980s[86,87]. It has been estimated that the current annual sales volume of microplate readers, multichannel pipettors, microstrips as well as other products developed on the basis of the vertical measurement principle together with their accessories already exceeds USD 2.0 billion annually[88,89].

The instruments based on vertical photometry have made possible the extensive research and fast development of the enzyme immunoassay (EIA) -technology

84 Finnpipette is a registered trademark of Labsystems Oy.
85 Multiskan is a registered trademark of Labsystems Oy.
86 Suovaniemi O. (1994). *Automated Instrumentation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors*, Ph.D. Thesis, University of Helsinki.
87 Tiusanen T. (1992). *Inner-Filter Correction with a Fluorometer-Based Multifunctional Instrument*, Ph.D. Thesis, University of Helsinki.

and related applications such as analyzing and screening of cancer and infectious diseases. During the past ten years, the EIA-technology has been followed by the rapid development of molecular biology techniques, such as the Polymerase Chain Reaction (PCR) -technique, which is used for the amplification of DNA. Vertical measurement applications have been widely used in recent years in connection with the PCR-technique and similar applications. Especially fast are growing the investments in equipment by companies specializing in automated molecular biology methods and the development of biologically active molecules. It has been estimated that these markets grow at an annual rate of 25 – 30%.

In order to serve its customer base comprehensively Biohit offers its customers complete analyzing systems, which comprise liquid handling products, diagnostic tests, analyzers, software as well as maintenance, calibration and training services. As to microplate instruments Biohit continues its co-operation with the U.S. company Bio-Tek, Inc. The instrument product range manufactured by the company is based on the vertical measurement principle and its applications invented by professor Suovaniemi at the end of the 1960s. As a system supplier Biohit aims to identify optimal product solutions for different market segments and via the sales of its products strengthen its global brand.

Product Range of Instruments and Software

Biohit's range of instruments comprises microplate readers and washers, and related software which support the performance and analysis of the result of Biohit's diagnostic tests. The instruments, which encompass microplate readers and washers, are equipped with an interface and connections to external control devices. As a result of the extensive menu-driven software the instruments can serve as stand-alone instruments or as part of a larger laboratory information management system (LIMS) when connected to a host device, such as a PC. Although the instruments are suited for multiple areas of use, e.g., biotechnology, cellular biology, clinical chemistry, environmental technology and food technology Biohit offers its customer base software for the easy and reliable performance of the GastroPanel.

The development of software, equipment and systems is based on Biohit's core technologies and especially customer applications in the area of diagnostics. The ease-of-use as well as the relevance and quality of information produced serve as primary aims for the development work. The know how related with instruments and the complete analyzing systems, and the experience and vision of the personnel form, on their part, a strong basis for the development of successful business.

Service Laboratory of Biohit

In August 2001 Biohit established a service laboratory, which received a permission from the State Provincial Office of Southern Finland, Department for Social and Health Affairs on May 8, 2001. The purpose of the service laboratory is to collect, first in Finland, patient samples, e.g., from health care centers, occupational health service centers, other medical centers as well as regional and central hospitals. Samples will be collected also abroad from general practitioners and other service laboratories. Biohit's service laboratory will also engage in the research and development of diagnostic tests and the analysis of different types of patient data in co-operation with scientific communities in Finland and abroad.

The purpose of Biohit's service laboratory is to promote the diagnostic tests and analyzing systems and, thus, to encourage the users of the laboratory service to begin making the necessary analyses themselves with the help of the analyzing system purchased from Biohit. In this way the customer will be able to receive the test results more easily, rapidly and at a lower cost.

The performance of the analyses as close as possible to the patient and doctor promotes decentralized laboratory diagnostics, which is usually the most optimal, and for this reason the most recommendable way. Decentralized laboratory diagnostics which promotes evidence-based medicine should be striven for not only for the benefit of the patient and the doctor but also since it decreases the costs of health care.

Biohit's service laboratory performs the following analyses:

- GastroPanel
- Helicobacter pylori IgG (S-HepyAbG), Pepsinogen I and II (S-Pepsin1 and S-Pepsin2), Gastrin-17 (S-Gastr17-S)
- Vitamin B12, fS-B12-vit, KL 1137
- Folat, fS-Folaat, KL 1416
- Folat from erythrocytes, fE-Folaat, KL1414
- Homocysteine, S-Hcyst, KL 1868
- Telomere-DNA IgG-antibodies, S-dsDNAAb
- Celiac panel: Gliadin IgA and IgG, tissue transglutaminase IgA, S-AGAAbA KL 3399, S-AGAAbG KL 3400, S-tTGAbA KL 1885
- Determination of lactase and saccharase from biopsies of the small intestine, Ts-Laktaas, KL 2182, Ts-Sakraas, KL 2601
- Microscopic examination of the endoscopic biopsy samples of the gastrointestinal tract, Ts-PADGast, KL 4043
- Cellular fibronectin (cFn -tumor marker for research use)

Instructions for taking samples and delivering the samples to the service laboratory can be ordered from Biohit Oyj, sales@biohit.com, fax: +358-9-773 86 200 or tel: +358-9-773 861.

Diagnostics in 2003

By the end of 2003 nineteen clinical evaluations related with the GastroPanel had been completed. Fourteen had been made in Europe, three in Asia and two in North America. The number of patients studied in the evaluations totalled 3,697. The results of the said evaluations have been published internationally in scientific articles and abstracts. The research results indicate that the GastroPanel examination is as specific as gastroscopy and the examination of biopsy samples in the evaluation of atrophic gastritis and related risks.

By the end of 2003 altogether twenty-five evaluations were in progress of which fifteen in Europe, four

88 McGrath & Associates, Inc. (1999).
89 Suovaniemi O. (1994). *Automated Instrumentation for Clinical and Research Laboratories – Innovations and Development of Vertical Light Beam Photometers and Electronic Pipettors*, Ph.D. Thesis, University of Helsinki.

in Asia, two in North America, one in South America, two in Africa, and one in the Near East. The number of patients to be studied in these on-going evaluations totals 29,424.

Biohit began negotiations to commence the following six evaluations: Three in Europe, one in North America, one in South America and one in the Near East. The number of patients to be studied totals 700.

The GastroPanel was taken into use in service laboratories in the following countries: Finland, France, Germany, Italy, Portugal, Spain, Sweden, the U.K and the U.S. During the financial year Biohit received the possibility for receiving patient reimbursement from the Social and Insurance Institution of Finland for the test kits of the GastroPanel.

In 2003 Biohit was awarded the following patents in the area of diagnostics:

- Japanese patent 3433231: “Method for Screening the Risk of Gastric Cancer.
- Russian patent 2204835: “Diagnosis of Early Gastric Cancer”.

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BOARD OF DIRECTORS´ REPORT

Biohit manufactures liquid handling products and accessories and diagnostic test systems for use in research, health care and industrial laboratories. Biohit's product range encompasses also instruments and related software, which together with the liquid handling products and diagnostic tests, enable to offer complete analyzing systems for the customers.

In the business area of liquid handling the main products of Biohit are electronic and mechanical liquid handling devices and their disposable tips. The diagnostic product range of Biohit encompasses the following tests: GastroPanel for diagnosing *Helicobacter pylori* -infection, atrophic gastritis as well as for screening the risk of gastric cancer and peptic ulcer from the blood samples; test for diagnosing lactose intolerance and test for the detection of systemic lupus erythematosus (SLE).

Net Sales

The net sales of the Biohit Group increased by 4% compared to the previous year and totalled MEUR 26.3 (MEUR 25.4). During the fourth quarter the net sales increased by 20% in comparison with the previous quarter, mainly due to new liquid handling products. The Group net sales increased especially in the U.S, and France. In 2003 the Group net sales was generated primarily from the sales of liquid handling products. Regarding diagnostics, Biohit is currently in the process for receiving the FDA Approval in the U.S., which enables Biohit to sell the diagnostic products also for the clinical use, in addition to research use.

The share of exports of Group net sales was approx. 94%. The primary market area continued to be Europe, which constituted approx. 57% of the Group net sales. Biohit considers North America and Asia to be important growth markets; especially in China the sales of liquid handling products demonstrated growth. The decrease of the USD exchange rate slowed down the growth of net sales.

Result

The loss for 2003 was MEUR 0.7 (MEUR 1.8 in 2002). The operating loss amounted MEUR 0.2 (MEUR 1.2 loss). The operating loss before goodwill amortization was MEUR 0.2 (MEUR 0.6 loss). The EBITDA increased by 97% and was MEUR 1.8 (MEUR 0.9).

The fixed expenses related to the diagnostics business had a negative impact on the group result.

The distribution of the Biohit products in Italy has been reorganized during the financial year, and it will be conducted in the future solely by local distributors. Therefore, the decision has been made to discontinue the activities of the Italian subsidiary of Biohit. One-time costs MEUR 0.5 relating to the discontinuation of this subsidiary are included in the 2003 income statement.

The operating expenses include the legal expenses (TEUR 150), which incurred during the third quarter.

The decision made on the third quarter of 2002 to prolong the goodwill amortization period related to Locus genex Oy improves the 2003 operating profit by MEUR 0.2 during the financial year when compared with the previous year.

The result of the parent company was affected considerably by goodwill amortization in excess of the planned depreciation by MEUR 2.1 supported by the impairment test.

The net financial expenses totalled MEUR 0.2 (MEUR 0.3).

The income taxes (MEUR 0.3) have been accounted for on the basis of the result for the financial year. However, deferred tax assets relating to the taxable losses have not been accounted for. MEUR 0.2 of the income taxes charged to the income statement result from the decrease in the deferred tax assets relating to the dissolution loss on Locus genex Oy.

Earnings per share were EUR -0.06 (EUR -0.14). The shareholders´ equity per share totalled EUR 1.08 (EUR 1.15).

Liquidity

The net cash flow provided by operating activities was MEUR 0.9 positive (MEUR 0.5 negative). At the end of the fiscal year the liquid assets of the Group totalled MEUR 1.1 (MEUR 1.4).

The equity ratio was 64.7% on December 31, 2003 (66.9%).

Investments

The gross investments totalled MEUR 1.2 (MEUR 1.6). The major part of the investments consisted of machinery and equipment acquired to the Kajaani plant for the automatization of liquid handling production, as well as of injection moulding tools used in the production of liquid handling devices.

The Group research and development expenditure totalled MEUR 1.4 (MEUR 1.8), i.e., 5.5% (7.1%) of net sales.

Administration and Personnel

During the financial year the following persons have been the members of the Board of Directors of Biohit Oyj: Professor Reijo Luostarinen as the Chairman and docent Arto Alanko, Professor Hannu Seristö, Professor Osmo Suovaniemi and Professor Mårten Wikström as members.

PricewaterhouseCoopers Oy have acted as the auditors, and Hannele Selesvuo as the responsible auditor.

The average number of personnel in 2003 totalled 298 (303) of which 174 (181) were employed by the parent company and 124 (122) by the subsidiaries.

Adoption of the IFRS (IAS) Standards

Biohit Group will adopt IFRS-based reporting as of 2005. In the 2005 interim reports the comparative figures for 2004 will be presented in accordance with IFRS.

During 2003 Biohit began the transition to IFRS. The new reporting system supporting IFRS reporting will be taken into full use at the beginning of 2004.

According to the preliminary assessment, most significant changes will relate to development expenses, subordinated loans and related interests and goodwill.

Prospects for 2004

The net sales of the Biohit Group is expected to develop favorably in 2004.

However, the growth of net sales is affected primarily by the market penetration of the diagnostic product range. In 2003 Biohit concluded distribution agreements related with diagnostics as well as concluded a significant number of national evaluations. Biohit forecasts that, if the company will be able to capture the market potential related to diagnostics in 2004, it most likely will have a significant effect on the net sales and profit for 2004 and for the following years.

In 2003 Biohit launched new liquid handling products, which have received a positive response from the customer base. Biohit estimates that the launch of the new pipettor models will have a positive impact on the net sales in 2004.

INCOME AND CASH FLOW STATEMENTS

INCOME STATEMENT January 1 – December 31		Group		Parent company	
EUR 1 000	Note	2003	2002	2003	2002
NET SALES	2.1.	26 259	25 354	17 019	14 994
Change in inventories of finished goods and work in progress		367	-216	73	-121
Other operating income		303	208	248	194
Materials and services	2.2.	-5 300	-4 644	-3 682	-2 855
Personnel expenses	2.3.	-10 739	-11 010	-6 363	-6 457
Depreciation and value adjustments	3.1.	-2 005	-2 140	-4 143	-1 308
Other operating expenses		-9 096	- 8 780	-5 562	-4 645
OPERATING PROFIT/LOSS		-213	-1 227	-2 409	-199
Financial income and expenses	2.4.	-250	-317	-175	-472
PROFIT/LOSS BEFORE INCOME TAXES		-462	-1 545	-2 584	-671
Income taxes	2.5.	-252	-282	0	-195
Minority interest		-4	26	0	0
NET PROFIT/LOSS		-719	-1 800	-2 584	-865

CASH FLOW STATEMENT January 1 – December 31	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
CASH FLOWS FROM OPERATING ACTIVITIES				
Profit/loss before extraordinary items	-435	-1 545	-2 585	-671
Adjustments:				
Depreciations	2 005	2 140	4 143	1 308
Financial income and expenses	250	317	175	472
Other adjustments	-50	0	-49	0
Cash flow before change in net working capital	1 770	912	1 684	1 109
CHANGE IN NET WORKING CAPITAL				
Increase (-)/ decrease (+) in non-interest bearing receivables	-419	-283	-1 006	-225
Increase (-)/ decrease (+) in inventories	483	613	-406	167
Increase (+)/decrease (-) in non-interest bearing liabilities	287	-461	445	-141
Funds generated before financial items and income taxes	1 155	781	717	911
Interests and other financial items paid	-399	-218	-200	-141
Interests received	180	147	55	233
Income taxes paid	-73	-1 164	0	-1 119
Net cash flow from operating activities (A)	863	-454	573	-115
NET CASH FLOW FROM INVESTING ACTIVITIES				
Investments in tangible and intangible assets	-1 142	-1 730	-1 045	-1 452
Proceeds from disposition of tangible and intangible assets	0	0	-150	0
Loans given	0	0	0	-430
Grants received	0	66	0	66
Repayments of loan receivables	0	0	203	110
Proceeds from the sales of other investments	120	0	120	110
Dividends received from investments	5	5	5	5
Net cash flow from investing activities (B)	-1 017	-1 659	-867	-1 701
NET CASH FLOW FROM FINANCING ACTIVITIES				
Proceeds from issuance of common stock	0	569	0	569
Increase in long-term debt	611	927	600	829
Repayments of long-term debt	-758	-467	-754	-477
Net cash flow from financing activities (C)	-147	1 028	-154	921
Net increase (+)/decrease (-) in cash and cash equivalents (A+B+C)	-301	-1 084	-448	-895
Cash and cash equivalents at January 1	1 374	2 458	936	1 831
Translation difference relating to cash and cash equivalents	-20	0	0	0
Cash and cash equivalents at December 31	1 054	1 374	489	936

BIOHIT

BALANCE SHEET

ASSETS January 1 – December 31		Group		Parent company	
EUR 1 000	Note	2003	2002	2003	2002
FIXED ASSETS AND OTHER LONG-TERM INVESTMENTS					
Intangible assets	3.1.1.	1 038	1 188	3 502	6 431
Goodwill	3.1.1.	2 638	3 049	0	0
Tangible assets	3.1.2.	6 195	6 425	5 693	5 755
Shares and holdings	3.2.	11	119	3 423	5 785
Total fixed assets and other long-t.investments		9 881	10 781	12 618	17 971
CURRENT ASSETS					
Inventories	3.3.	4 074	3 600	2 406	1 999
Deferred tax asset	3.7.	1 141	1 320	0	0
Long-term receivables	3.4.	0	0	292	477
Short-term receivables	3.4.	5 724	5 339	6 450	5 644
Cash at bank and in hand		1 054	1 374	489	936
Total current assets		11 993	11 633	9 637	9 057
TOTAL ASSETS		21 875	22 414	22 255	27 028

SHAREHOLDERS' EQUITY AND LIABILITIES January 1 – December 31		Group		Parent company	
EUR 1 000	Note	2003	2002	2003	2002
SHAREHOLDERS' EQUITY					
Share capital	3.5.1.	2 199	2 199	2 199	2 199
Share premium fund	3.5.1.	15 425	15 425	15 425	15 425
Accumulated profit/loss from prior years	3.5.1.	-2 869	-1 003	268	1 133
Profit/loss for the year	3.5.1.	- 719	-1 800	-2 584	-865
Capital loans	3.5.4.	1 243	1 243	1 243	1 243
Total shareholders' equity		15 280	16 066	16 552	19 136
MINORITY INTEREST		65	75	0	0
UNTAXED RESERVES	3.6.	0	0	359	359
LIABILITIES					
Deferred tax liability	3.7.	104	104	0	0
Long-term liabilities	3.8.1.	2 302	2 535	2 179	2 345
Short-term liabilities	3.8.2.	4 124	3 634	3 166	5 188
Total liabilities		6 530	6 273	5 345	7 534
TOTAL SHAREHOLDERS' EQUITY AND LIABILITIES		21 875	22 414	22 255	27 028

NOTES TO THE FINANCIAL STATEMENTS'

1. ACCOUNTING PRINCIPLES

The financial statements have been prepared in accordance with Finnish Accounting Act.

Preparation of the financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affects the amounts and figures in the financial statements. Actual results could differ from those estimates.

Amounts are presented in euros and are based on the original value of transactions.

PRINCIPLES OF VALUATION AND PERIODIZATION OF REVENUES AND COSTS

Valuation of Fixed Assets

Fixed assets are recorded in the balance sheet at historical cost net of grants received and depreciation. Depreciation is calculated on straight-line basis over the useful life of the assets.

The useful life times are:

Intangibles	5 – 10 years
Goodwill (group)	3 – 20 years
Goodwill (parent)	10 years
Buildings	20 years
Other capitalized costs	5 – 10 years
Machinery and equipment	3 – 10 years

The board of Biohit has 27.8.2002 decided to prolong the goodwill amortization period related to Locus genex Oy from seven to 20 years. In 2002 the goodwill amortization totalled MEUR 0.4. This corresponds with the amortization made on the first half of 2002 based on the original 7 years' amortization period.

The amortization period of the goodwill at the parent company, which consists of the patents and liquidation loss transferred to Biohit Oyj as a result of liquidation of Locus genex Oy, was correspondingly prolonged from 5 to 10 years. The current amortization period agrees with the amortization period in taxation. The change was carried out retroactively so that no amortizations were recorded in 2002.

The result of the parent company was affected considerably by goodwill amortization in excess of the planned depreciation by MEUR 2.1 supported by impairment test.

Valuation of Inventories
Inventories are stated at the lower of cost, on a first-in-first-out (FIFO) basis, or net realizable value. The value of finished goods includes an appropriate proportion of production overheads in addition to the direct costs.

R & D Expenses
R & D costs are recorded as expenses when occurred.

Revenue Recognition
Net sales are calculated as gross sales less indirect sales taxes and discounts. Revenues from products and services are recognized upon delivery.

Maintenance and Repairs
Costs for maintenance and repairs are recorded as expenses when occurred. The costs of renovating rented premises have been capitalized under other capitalized expenses and will be depreciated on a straight-line basis over the remaining rental period.

Pensions
The pension schemes and any additional pension benefits required by Finnish law are arranged through pension insurance companies. Pension costs are charged to the income statement for the period when earned. In foreign subsidiaries pension costs are accounted for in accordance with the local practice.

Foreign Currency Translation
Receivables and liabilities in foreign currencies are translated into euro at the exchange rate quoted by the European Central Bank on the balance sheet date. Exchange gains and losses are recorded to profit and loss account.

ACCOUNTING PRINCIPLES USED IN THE CONSOLIDATED FINANCIAL STATEMENTS

Scope of Consolidated Financial Statements
The consolidated financial statements include Biohit Oyj and all companies in which the Group holds more than 50% of the voting rights. Subsidiary companies are included in the consolidated financial statements from the date of acquisition.

Intragroup Shareholdings
The consolidated financial statements have been prepared using the purchase method. The difference between the acquisition cost and the shareholders' equity corresponding to the acquired holding is presented as goodwill.

Intragroup Transactions and Margins
Intragroup transactions, unrealized internal profits, receivables and debts as well as intragroup distribution of profits are eliminated in the consolidated financial statements.

Translation Differences
The income statements of foreign group companies are translated into euro at the average exchange rate for the year and the balance sheets at the exchange rate on the balance sheet date. Differences arising from the translation as well as those from translating shareholders' equity are recorded in the consolidated financial statements under "Accumulated profit/loss from prior years".

Deferred Taxes
Deferred income tax liabilities and receivables have been accounted for on temporary differences based on tax rates enacted at the balance sheet date. The deferred tax liability has been fully provided for while the deferred tax assets have been stated at the recoverable amount. No deferred tax assets have been recognised on tax loss carry forwards.

2. NOTES TO THE INCOME STATEMENT

2.1. Net sales by Geographical Area		Group		Parent company	
EUR 1 000	Note	2003	2002	2003	2002
Finland		1 517	1 403	1 517	1 705
Other Europe		13 540	12 998	8 745	8 059
North and South America		5 512	5 205	3 683	2 771
Asia		3 500	3 186	2 908	2 351
Other countries		2 190	2 561	166	108
Total		26 259	25 354	17 019	14 994

2.2. Materials and Services	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Materials				
Purchases during the year	5 199	4 299	3 809	2 769
Change in inventories	-341	46	-341	45
Total materials	4 858	4 344	3 468	2 814
External services	442	299	214	41
Total materials and services	5 300	4 644	3 682	2 855

2.3. Personnel Expenses and Number of Personnel	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Salaries and wages	8 550	8 780	5 097	5 197
Pension expenses	1 079	1 136	852	828
Other personnel expenses	1 110	1 094	414	432
Total	10 739	11 010	6 363	6 457

Salaries and Fees of the Management

The salaries of the Group's managing directors totalled TEUR 554 (TEUR 625 in 2002). The fees to the members of the Board of Directors were TEUR 64 (TEUR 49 in 2002) in the parent company and Group. Any other notable pension arrangements other than those laid down by law have not been made with the managing directors of Group companies.

	Group		Parent company	
Personnel *)	2003	2002	2003	2002
Office personnel	200	211	76	89
Factory personnel	98	92	98	92
Personnel average	298	303	174	181
Personnel at end of the year	300	283	173	158

*) dismissals are not included

2.4. Financial Income and Expenses	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Dividend income from outside the Group	5	5	5	5
Interest income from long-term investments				
From Group companies			40	132
Other interest and financial income:				
From Group companies			0	17
From others	180	147	15	97
Total	180	147	55	245
Value adjustments of shares and holdings			-1	-275
Interest expense and other financial expenses:				
To Group companies			-9	-2
To others	-435	-469	-226	-444
Total financial income and expenses	-250	-317	-175	-472
Net foreign exchange losses included in "Financial income and expenses"	113	168	78	245

2.5. Income Taxes	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Current income taxes on ordinary operations	-73	-85	0	-5
Change in deferred income tax liability/assets	-179	-197	0	-190
Total	-252	-282	0	-195

3. NOTES TO THE BALANCE SHEET

3.1. Tangible and Intangible Assets

3.1.1. Intangible Assets Group EUR 1 000	Intangibles	Goodwill	Other capitalized expenses	Total
Acquisition cost at beginning of year	1 131	6 547	1 235	8 913
Additions	109	0	56	165
Acquisition cost at end of year	1 240	6 547	1 291	9 078
Accumulated depreciation and value adjustments at beginning of year	-506	-3 498	-671	-4 675
Depreciation for the year	-109	-411	-208	-728
Accumulated depreciation and value adjustments at end of the year	-615	-3 909	-879	-5 403
Net book value at end of year	625	2 638	412	3 675

3.1.1. Intangible Assets Parent Company EUR 1 000	Intangibles	Goodwill	Other capitalized expenses	Total
Acquisition cost at beginning of year	1 131	6 558	1 043	8 732
Additions	109	0	45	154
Acquisition cost at end of year	1 240	6 558	1 088	8 886
Accumulated depreciation and value adjustments at beginning of year	-506	-1 312	-483	-2 301
Depreciation for year	-109	- 2 781	-194	-3 084
Accumulated depreciation and value adjustments at end of the year	-615	-4 092	-677	-5 385
Net book value at end of year	625	2 466	411	3 502

Goodwill in parent company consists of patents (TEUR 5 045) transferred as a result of the dissolution of Locus genex Oy and liquidation loss (TEUR 1 513).

3.1.2. Tangible Assets Group

EUR 1 000	Buildings	Machinery and Equipment	Total
Acquisition cost at beginning of year	2 309	8 708	11 017
Additions	0	1 086	1 086
Decreases	0	-258	-258
Translation differences	0	-39	-39
Acquisition cost at end of year	2 309	9 498	11 806
Accumulated depreciation and value adjustments at beginning of year	-259	-4 333	-4 592
Accumulated depreciation on disposed assets	0	258	258
Depreciation during year	-115	-1 162	-1 277
Accumulated depreciation and value adjustments at end of the year	-374	-5 237	-5 611
Net book value at end of year	1 934	4 261	6 195

3.1.2. Tangible Assets Parent company

EUR 1 000	Buildings	Machinery and Equipment	Total
Acquisition cost at beginning of year	2 309	7 363	9 672
Additions	0	1 062	1 062
Disposals	0	-258	-258
Acquisition cost at end of year	2 309	8 168	10 477
Accumulated depreciation and value adjustments at beginning of year	-259	- 3 658	-3 917
Accumulated depreciation on disposed assets	0	192	192
Depreciation during year	-115	-943	-1 059
Accumulated depreciation and value adjustments at end of the year	-374	-4 409	-4 784
Net book value at end of year	1 934	3 759	5 693

The book value of production machinery and equipment is TEUR 3 248.

3.2. Shares and Holdings

Group

EUR 1 000

	Shares
Book value at beginning of year	119
Disposals	-108
Book value at end of year	11

Parent company

EUR 1 000	Shares Group companies	Other shares	Loans receivable from companies within the Group	Total
Book value at beginning of year	4 384	117	1 284	5 785
Additions	1 617	0	0	1 618
Disposal	-2 588	-107	-1 284	-3 979
Book value at end of year	3 413	10	0	3 423

The decrease in group shareholdings is related to the voluntary dissolution of Locus genex Oy. The increase in the group shareholdings consists of conversion of loan receivables and related accrued interest from Biohit Inc to equity investment.

Decrease in other sharehodings consists of sold Nordea Oyj and Elisa Oyj shares.

Group Companies 31.12.2003	Group holding	Parent company shareholding
Biohit Ltd., Great Britain	100%	100%
Biohit S.A., France	91%	91%
Biohit s.r.l., Italy	90%	90%
Biohit Deutschland GmbH, Germany	100%	100%
Biohit Japan Co., Ltd., Japan	100%	100%
Biohit Inc., USA	95%	95%
Biohit OOO, Russia	100%	100%
Oy Finio Ab, Finland	100%	100%
Vantaan Hienomekano Oy, Finland	100%	100%

Oy Finio AB and Vantaan Hienomekano Oy were not operating during 2003. Finnbio Ltd was sold and the Russian business operations transferred to Biohit OOO. The voluntary liquidation process of Locus genex Oy was finalised on December 2003.

3.3. Inventories

	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Materials	1 333	953	1 328	995
Finished products/goods	2 741	2 640	1 078	1 004
Advance payments	0	8	0	0
Total inventories	4 074	3 600	2 406	1 999

3.4. Receivables

	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
LONG-TERM RECEIVABLES				
Receivables from Group companies				
Loans receivable	0	0	292	477
SHORT-TERM RECEIVABLES				
Receivables from Group companies				
Accounts receivable	0	0	3 877	3 445
Loans receivable	0	0	107	113
Other receivables	0	0	0	198
Receivables from other companies				
Accounts receivable	5 068	4 639	2 154	1 571
Other receivables	351	285	175	170
Prepayments and accrued income	305	415	137	149
Total short-term receivables	5 724	5 339	6 450	5 644

3.5. Shareholders' Equity

3.5.1. Shareholders' Equity	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Share capital at beginning of year	2 199	2 149	2 199	2 149
Share issue	0	50	0	50
Share capital at end of year	2 199	2 199	2 199	2 199
Share premium fund at beginning of year	15 425	14 906	15 425	14 906
Premium from share issue	0	519	0	519
Share premium fund at end of year	15 425	15 425	15 425	15 425
Profit/loss from prior years at beginning of year	-2 803	-832	268	1 133
Translation difference	-67	-171	0	0
Profit/loss from prior years at end of year	-2 869	-1 003	268	1 133
Loss for year	-719	-1 800	-2 584	-865
Capital loans at beginning and at end of year	1 243	1 243	1 243	1 243
Total shareholders' equity	15 280	16 066	16 552	19 136

3.5.2. Distributable equity at 31 December	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Profit/loss from prior years	-2 869	-1 003	268	1 133
Loss for the year	-719	-1 800	-2 584	-865
Unrecorded interest on capital loans	-539	-480	-539	-480
Accelerated depreciation included in shareholders´ equity	-255	-255	0	0
Total	-4 382	-3 537	-2 855	-213

The calculation above demonstrates that, on the basis of the Companies Act, Biohit does not have distributable earnings as at 31.12.2003.

3.5.3. Share capital of Parent company	2003		2003		2002	
	No. of shares	EUR	% of shares	% of votes	No. of shares	EUR
A-shares (20 votes per share)	3 875 500	658 835	30.0	89.5	3 875 500	658 835
B-shares (1 vote per share)	9 062 127	1 540 562	70.0	10.5	9 062 127	1 540 562
Total	12 937 627	2 199 397	100.0	100.0	12 937 627	2 199 397

The shares of Biohit Oyj comprise of A and B shares. At meetings of shareholders shares of series A entitle to 20 votes each and shares of series B to one vote each. In distribution of dividends, the dividend payable on shares of series B shall be higher by two per cent (2%) of the nominal value compared with the dividend payable on shares of series A.

3.5.4. Capital loans

On December 31, 2003, the Parent company and Group held TEUR 1 243 in capital loans. The terms for the capital loans conform to section 5, paragraph 1 of the Finnish Companies Act. TEUR 880 of the capital loans are from the company's main shareholders.

3.6. Appropriations	Parent company	
EUR 1 000	2003	2002
Untaxed reserves	359	359

The untaxed reserves derive from the accelerated depreciation.

3.7. Deferred income tax liabilities and assests	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Deferred income tax assets				
From consolidation entries	1 141	1 320	0	0
Deferred income tax liabilities				
From temporary differences	104	104	0	0
Net	1 037	1 216	0	0

Deferred income tax assets from consolidation entries include taxes paid as a result of dissolution of Locus genex Oy of TEUR 878 which are deferred in the group accounts over the remaining amortization period of 15 years of the goodwill relating to Locus genex Oy.

Cumulative tax losses of the group companies, including the losses of the current year, amount to approximately MEUR 2,9. The relating deferred tax assets, MEUR 0,8, has not been accounted for the financial statements.

3.8. Liabilities

3.8.1. Long-term Liabilities	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Loans from financial institutions	1 623	1 720	1 564	1 588
Other long-term debt	679	815	615	757
Total long-term liabilities	2 302	2 535	2 179	2 345
Debts falling due in more than five years				
Loans from financial institutions	0	119	0	85
Other long-term debt	237	284	237	284

3.8.2. Short-term Liabilities	Group		Parent company	
EUR 1 000	2003	2002	2003	2002
Loans from financial institutions	928	801	897	801
Advances received	70	146	21	2
Accounts payable	1 287	837	844	430
Other liabilities	443	677	143	117
Accrued liabilities	1 396	1 172	1 009	999
Liabilities from Group companies				
Accounts payable	0	0	52	51
Other short term liabilities	0	0	200	2 789
Total short-term liabilities	4 124	3 634	3 166	5 189

Accrued liabilities consist mainly of holiday pay and related social security accruals.

4. OTHER NOTES

4.1. Pledges given, Commitments and Contingencies

Pledges given	Group		Parent company	
1 000 EUR	2003	2002	2003	2002
Loans for which mortgages and pledges have been given				
Loans from financial institutions	2 037	2 143	2 037	2 143
Corporate mortgages	3 389	3 389	3 389	3 389
Pledges on leaseholds	1 500	1 500	1 500	1 500
Other long-term liabilities	710	757	710	757
Mortgages on real estate	757	757	757	757

The parent company has given pledges of MEUR 0.4 on behalf of Group companies.

Leasing commitments	Group		Parent company	
1 000 EUR	2003	2002	2003	2002
Due for payment in the following year	1 142	1 389	685	690
Due for payment at a later date	1 629	2 723	1 195	1 744
Total	2 771	4 112	1 880	2 434

Leasing commitments include mainly fixed-term leasing and rental agreements which are effective more than one year.

Interest on capital loans

On December 31, 2003, accumulated, unrecorded interest on capital loans was TEUR 539 (TEUR 480) for the parent company and for the Group.

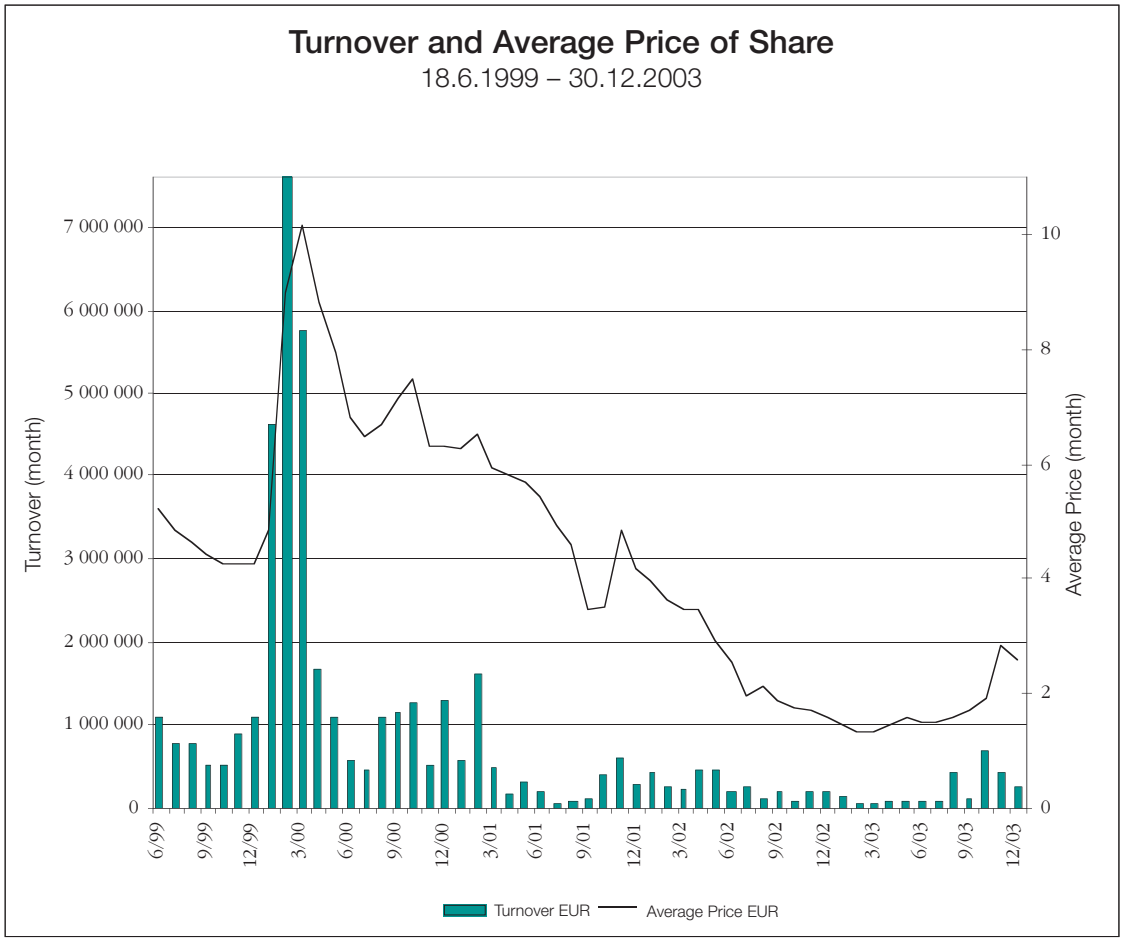
Derivative contracts

The group has no off-balance sheet financial instruments.

4.2 Ratios

Financial ratios	1999	2000	2001	2002	2003
Net sales	20 551	24 247	25 545	25 354	26 259
Increase in net sales %	21.7%	18.0%	5.4%	-0.7%	3.6%
Operating profit/loss	1 332	-482	237	-1 227	-213
% of net sales	6.5%	-2.0%	0.9%	-4.8%	-0.8%
Profit/loss before extraordinary items and income taxes	825	-580	55	-1 545	-462
% of net sales	4.0%	-2.4%	0.2%	-6.1%	-1.8%
Profit/loss before voluntary provisions and taxes	1 162	-341	55	-1 545	-462
% of net sales	5.7%	-1.4%	0.2%	-6.1%	-1.8%
Return on equity, %	3.8%	-4.6%	-1.3%	-11.7%	-4.9%
Return on investment, %	8.5%	-0.8%	2.0%	-5.5%	-0.2%
Equity ratio, %	66.0%	66.9%	65.7%	66.9%	64.7%
Investments in fixed assets	1 271	6 208	2 212	1 578	1 190
% of net sales	6.2%	25.6%	8.7%	6.2%	4.5%
Research and development	1 270	1 698	2 114	1 809	1 447
% of net sales	6.2%	7.0%	8.3%	7.1%	5.5%
Total assets	24 699	24 626	24 996	22 414	21 875
Personnel, average	184	222	289	303	298

Ratios per share	1999	2000	2001	2002	2003
Earnings per share, EUR	0.04	-0.06	-0.02	-0.14	-0.06
Equity per share, EUR	1.33	1.30	1.28	1.15	1.08
Price/earnings (P/E)	102	-101	-233	-10	-45
Dividend per share, EUR	0	0	0	0	0
Dividend per earnings, %	0	0	0	0	0
Effective yield of shares, %	0	0	0	0	0
Price development of B-shares, EUR					
- average price	4.54	7.43	5.35	2.56	1.85
- lowest price	3.75	4.20	3.00	1.40	1.22
- highest price	6.00	13.50	7.20	4.40	3.30
- price on December 31	4.13	6.20	4.28	1.41	2.50
Market price for the entire capital stock, EUR 1000 (assuming that market price of A-share is the same as B-share's)	50 653	78 389	54 114	18 242	32 344
Development of exchange of B-shares, pcs 1000	1 240	3 647	909	1 178	1 287
- % of total amount of shares	16.6%	41.9%	10.4%	13.2%	14.2%
Average number of shares, adjusted for share issues	11 354 957	12 573 123	12 643 377	12 827 781	12 937 627
Number of shares at the balance sheet date, adjusted for share issues	12 264 537	12 643 377	12 643 377	12 937 627	12 937 627



4.3 Shares and shareholders

Shares and voting rights

The shares of Biohit Oyj are divided into A and B shares. At shareholders' meetings the series A is entitled to 20 votes each and series B shares to one vote each. As to the distribution of dividends, the dividend payable on series B shares shall be two per cent (2%) higher of the nominal value compared with the dividend payable on series A shares.

Share capital of the parent company	2003		2003		2002	
	No. of shares	EUR	% of shares	% of votes	No. of shares	EUR
A-shares (20 votes per share)	3 875 500	658 835	30.0	89.5	3 875 500	658 835
B-shares (1 vote per share)	9 062 127	1 540 562	70.0	10.5	9 062 127	1 540 562
Total	12 937 627	2 199 397	100.0	100.0	12 937 627	2 199 397

According to the Articles of Association, the Company's minimum share capital is EUR 1 063 101.29 and the maximum share capital EUR 4 252 405.16 within which limits the share capital can be raised or lowered without amending the Articles of Association.

The Company does not possess own shares. The Board of Directors does not have outstanding authorization to issue shares, convertible bonds or option loans or acquire shares in the Company. The Company does not currently have an option plan.

Ownership of shares by sector on Dec. 31, 2003

A-shares	Number of shareholders		Number of shares	
	pieces	%	pieces	%
1. Companies	2	22.22	919 990	23.74
2. Households	7	77.78	2 955 510	76.26
Total	9	100.00	3 875 500	100.00

B-shares	Number of shareholders		Number of shares	
	pieces	%	pieces	%
1. Companies	205	4.79	2 134 312	23.55
2. Households	5	0.12	130 913	1.44
3. Public organizations	1	0.02	406 700	4.49
4. Non-profit organizations	16	0.37	73 530	0.81
5. Households	4 032	94.12	6 245 170	68.92
6. Foreign	25	0.58	65 910	0.73
Shares which are not entered into the book-entry system			5 592	0.06
Total	4 284	100.00	9 062 127	100.00
Nominee-registered shares	7		126 430	1.4

Ownership according to the number of shares owned on December 31, 2003

A-shares	Number of shareholders		Number of shares	
	pieces	%	pieces	%
1-1 000	1	11.11	10	0.00
1 001-5 000	0	0.00	0	0.00
5 001-10 000	0	0.00	0	0.00
10 001-50 000	1	11.11	19 990	0.52
Over 50 000	7	77.78	3 855 500	99.48
Total	9	100.00	3 875 500	100.00

B-shares	Number of shareholders		Number of shares	
	pieces	%	pieces	%
1-1 000	3 659	85.27	1 285 624	14.19
1 001-5 000	512	11.93	1 109 399	12.24
5 001-10 000	71	1.65	536 700	5.92
10 001-50 000	32	0.75	570 308	6.29
Over 50 000	17	0.40	5 554 504	61.29
Total	4 291	100.00	9 056 535	99.94
Shares which are not entered into the book-entry system			5 592	0.06
Total			9 062 127	100.00

Major shareholders on December 31, 2003

10 major shareholders according to number of shares	A-shares	B-shares	Total no. of shares	%
Suovaniemi, Osmo	2 285 340	2 267 072	4 552 412	35.19
Erja-Yhtymä Oy	900 000		900 000	6.96
Suovaniemi, Ville	208 280	371 300	579 580	4.48
Suovaniemi, Joel	208 280	337 500	545 780	4.22
Härkönen, Matti	57 200	449 300	506 500	3.91
Suovaniemi, Oili	121 600	296 135	417 735	3.23
Etera Keskinäinen Eläkevakuutusyhtiö		406 700	406 700	3.14
Suovaniemi, Vesa	74 800	271 817	346 617	2.68
Etra-Invest Oy Ab		341 000	341 000	2.64
Adlercreutz, Herman		240 000	240 000	1.86

10 major shareholders according to number of votes	A-shares	B-shares	Total no. of votes	%
Suovaniemi, Osmo	45 706 800	2 267 072	47 973 872	55.41
Erja-Yhtymä Oy	18 000 000		18 000 000	20.79
Suovaniemi, Ville	4 165 600	371 300	4 536 900	5.24
Suovaniemi, Joel	4 165 600	337 500	4 503 100	5.20
Suovaniemi, Oili	2 432 000	296 135	2 728 135	3.15
Suovaniemi, Vesa	1 496 000	271 817	1 767 817	2.04
Härkönen, Matti	1 144 000	449 300	1 593 300	1.84
Tech Know Oy Ltd	399 800	141 300	541 100	0.63
Etera Keskinäinen Eläkevakuutusyhtiö		406 700	406 700	0.47
Etra-Invest Oy Ab		341 000	341 000	0.39

Ownership by management on December 31, 2003
The members of the Board and the President of the Company owned a total of 2 285 340 A-shares and 2 351 308 B-shares on December 30, 2003.This in total stands for 35.84% of all shares and 55.51% of the votes in the Company.

Formulas used in calculating key ratios

Return on equity, %

$$\frac{\text{Profit before extraordinary items – income taxes for the period} \times 100}{\text{Shareholders´equity – capital loans + minority interest (average over the year)}}$$

Return on capital employed, %

$$\frac{\text{Profit before extraordinary items + interest and other financial expenses} \times 100}{\text{Total assets – non-interest-bearing liabilities (average over the year)}}$$

Equity ratio, %

$$\frac{\text{Shareholders´equity – capital loans + minority interest} \times 100}{\text{Total assets – advance payments received}}$$

Earnings per share, EUR

$$\frac{\text{Profit before extraordinary items – income taxes for the period – minority interest}}{\text{Average number of shares, adjusted for share issue}}$$

Equity per share, EUR

$$\frac{\text{Shareholders´equity – capital loans}}{\text{Number of shares at the balance sheet date, adjusted for share issues}}$$

Dividend per share, EUR

$$\frac{\text{Dividend for the period}}{\text{Number of shares at the balance sheet date, adjusted for share issues}}$$

Dividend per earnings, %

$$\frac{\text{Dividend/share} \times 100}{\text{Earnings per share}}$$

Effective dividend yield, %

$$\frac{\text{Dividend, adjusted for share issue/share} \times 100}{\text{Stock exchange price on December 31, adjusted for share issues}}$$

Price/earnings, (P/E)

$$\frac{\text{Stock exchange price on December 31, adjusted for share issues}}{\text{Earnings per share}}$$

PROPOSAL OF THE BOARD OF DIRECTORS AND AUDITORS´ REPORT

Proposal for the handling of the loss
The Company does not have distributable earnings.
The Board of Directors proposes that no dividends be paid and that the loss for the period of EUR 2 584 083.19 be transferred to the retained profit/loss account from previous years.

Helsinki, February 12, 2004

Reijo Luostarinen
Chairman of the Board
of Directors

Osmo Suovaniemi
Member of the Board
of Directors
Managing Director

Mårten Wikström
Member of the Board
of Directors

Arto Alanko
Member of the Board
of Directors

Hannu Seristö
Member of the Board
of Directors

AUDITORS' REPORT

To the shareholders of Biohit Oyj

We have audited the accounting records, the financial statements and the corporate governance of Biohit Oyj for the financial period 1.1.-31.12.2003. The financial statements, which include the report of the Board of Directors, consolidated and parent company income statements, balance sheets and notes to the financial statements, have been prepared by the Board of Directors and the Managing Director. Based on our audit we express an opinion on these financial statements and the corporate governance of the parent company.

We have conducted our audit in accordance with the Finnish Standards on Auditing. Those standards require that we perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used as well as evaluating the overall financial statement presentation. The purpose of our audit of corporate governance is to examine that the members of the Board of Directors and the Managing Director of the parent company have legally complied with the rules of the Companies' Act.

In our opinion the financial statements have been prepared in accordance with the Accounting Act and other rules and regulations governing the preparation of financial statements. The financial statements give a true and fair view, as defined in the Accounting Act, of the result of operations as well as the financial position of the group and the parent company. The financial statements including the consolidated financial statements can be adopted and the members of the Board of Directors and the Managing Director of the parent company can be discharged from liability for the financial period audited by us. The proposal by the Board of Directors regarding the handling of the loss for the financial period is in compliance with the Companies' Act.

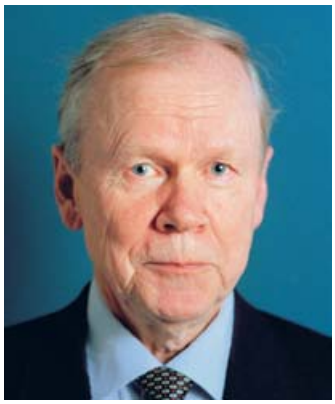
Helsinki, March 11, 2004

PricewaterhouseCoopers Oy
Authorised Public Accountants

Hannele Selesvuo
Authorised Public Accountant

ADMINISTRATION AND SCIENTIFIC ADVISOR

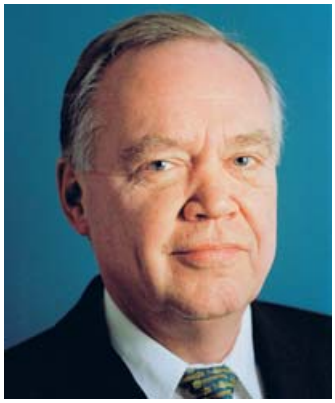
BOARD OF DIRECTORS



Reijo Luostarinen, D.Sc.(Econ.), Professor. *Internationalization and Strategic Planning*. Current Chairman of the Board of Biohit and member of the Board of Biohit since 1993. Professor of International Business at the Helsinki School of Economics (HSE). Head of the faculty and Director of the International Business (IB) Program and Director of the Center for International Business Research 1981-2003. Vice-Rector of HSE 1990-1995. Docent at the Helsinki University of Technology and the University of Vaasa. Visiting professor or guest lecturer in 23 different countries. Asla Fulbright scholar at the University of Michigan. President of the European International Business Academy and Regional Chairman of the Academy of International Business (USA) in Europe 1989-1990. Board member of six scientific councils and foundations. Chairman of four international academic conferences. Senior advisor of international business for different U.N.-organizations, some governments and ministries. Owner of two consulting firms, chairman and shareholder of three companies, and board member of altogether ten companies in 1980-1997. Author of fifteen books, chapters in five books, editor of two books and author of seventy articles, working papers and research papers. Editorial board member of six international scientific journals. International operations and global business strategy expert in companies located in different countries. Holdings in Biohit on December 31, 2003: 76,500 B-shares.

Arto Alanko, M.D., Ph.D., Docent. *Co-operation with Health Care Units*. Member of the Board of Biohit since 2001. Docent Alanko has acted since 2001 as the Provincial Medical Officer of Southern Finland and as of 2002 the Director of the Regional Unit for Health and Social Affairs. Between 1997-2000 he served as the Director of Jorvi Hospital and participated, e.g., in the preparation and development of the strategy for the hospital district of Helsinki and Uusimaa. Previously docent Alanko has acted, e.g., as the Administrative Medical Officer of the Helsinki University Central Hospital, as the Senior Medical Officer of the Hospital Department of the National Board of Health, as researcher in surgical oncology and as surgical and administrative consultant in various hospitals. The quality management project directed by him at the Helsinki University Central Hospital won the Arthur Andersen / Ed Crosby -prize granted by the International Hospital Federation (IHF) for a good managerial innovation in 1995. Docent Alanko has also participated in numerous national work groups. The number of scientific articles and publications prepared by docent Alanko totals 140. Holdings in Biohit on December 31, 2003: 7,400 B-shares.

Hannu Seristö, D.Sc. (Econ.), Professor. *International Marketing and Competitive Strategies*. Member of the Board of Biohit since 2002. Professor of International Business at the Helsinki School of Economics (HSE). Prof. Seristö received his Master's degree in 1987 and worked in managerial positions of international business and international marketing at Finnair Oy, McKinsey & Co. Inc. and Suunto Oy. He started doctorate studies in 1992, received his licentiate degree in 1993, and earned his doctorate from HSE in 1995 after research work at Cranfield University in England. Prof. Seristö's teaching and research focuses on international business strategies, international marketing, and business in the context of the European Union. He is the chairman of the board of the HSE International Center, which provides the leading Master of Business Administration (MBA) Program in the Nordic countries. Holdings in Biohit on December 31, 2003: 336 B-shares.



Mårten Wikström, M.D., Ph.D., Academy Professor. *Development of Co-operation with Scientific and Research Communities*. Member of the Board of Biohit since 1997. Professor of Medical Chemistry at the University of Helsinki. Academy professor since 1996. Prof. Wikström is actively engaged in basic scientific research (biochemistry, biophysics, molecular biology) at the University of Helsinki where he directs the Helsinki Bioenergetics Group, an international research team. Moreover, he acts as the Research Director of the program on structural biology and biophysics at the Institute of Biotechnology, University of Helsinki. Prof. Wikström has over 160 original publications on basic research in internationally renowned journals and he has received several scientific awards, e.g., the Anders Jahre Medical Prize for young researchers (1984), the A. I. Virtanen Prize (1989), the Matti Äyräpää Prize (1993), and the main Anders Jahre Medical Prize (1996). He is member of Societas Scientarum Fennica and foreign member of the Royal Swedish Academy of Sciences. In 1985-1989 he served as the Director of Research and as Operative Director at Eflab Oy and Labsystems Oy. No shareholdings on December 31, 2003.

Osmo Suovaniemi, M.D., Ph.D., Professor. *Management and Development of the Operative Activities of the Group*. *Development of the Liquid Handling and Diagnostic Product Ranges.* Founder, President and CEO and member of the Board of Biohit. His background as the founder, main shareholder, Chairman and CEO of Labsystems Oy and Eflab Oy until 1986, and as a major innovator of the products of those companies, demonstrates his experience and skills in this field of business. He received the M.D. in 1972 and the Ph.D. in 1994, both from the University of Helsinki, Finland. He has also completed the JOKO Executive Education study program at the Helsinki School of Economics in 1976-1977 and an education program at the Finnish Institure of Management (LIFIM) in 1982. In 1976 he received an award from the Finnish Foundation of Inventors for the single- and multichannel Finnpipette invention. He has served as board member, Vice-Chairman and Chairman of the General Industry Group in Finland between 1978-1986 and as board member of the Confederation of Finnish Industry in 1986. In 1984 the Finnish economic reporters awarded him an honorary prize for his economic achievements in 1983. Prof. Suovaniemi has been awarded 66 patents in Finland and a few hundred worldwide, mainly in the fields of medical diagnostics, optics and mechanics. He received an honorary award from the Finnish Board of Patents and Registration on November 19, 2002. On June 29, 2002, which was the 160th jubilee of granting the first patent in Finland, Suovaniemi possessed most Finnish patents. Suovaniemi received the honor and name of professor from the President of Finland in 2002. In 2003 he was appointed as the member of the Academy of Technical Sciences. Holdings in Biohit on December 31, 2003: 2,285,340 A-shares and 965,207 B-shares.

MANAGEMENT TEAM

Osmo Suovaniemi. *President & CEO.*

Erik Forsblom. *Diagnostics*. M.Sc. (Biochemistry). With Biohit since 1990. Mr. Forsblom holds an over 20 years' experience in the field of clinical chemistry. Between 1973-1981 worked as laboratory technician and chemist (assistant chemist and departmental chemist) at the Clinical Laboratory Center and at the United Clinical Laboratories in Helsinki. In 1981 joined Labsystems Oy as research chemist. Between 1984 and 1988 acted as Production Manager of the Diagnostics Division and between 1988-1990 as Assistant Director of the Diagnostics Division of Labsystems Oy. Upon joining Biohit in 1990 acted as Marketing Manager/Regional Export Manager between 1990-1996.

Jussi Heiniö. *Administration and Legal Affairs*. LL.M. With Biohit since 1997. Graduated from the Faculty of Law at the University of Helsinki in 1988. Between 1988-1992 acted first as an assistant lawyer and from 1992 as an Attorney-at-Law at Law Office Matti Oksala Ky. Between 1989-1990 worked as a junior lawyer undergoing court training and later on as a judge in the District Court of Vantaa, Finland.

Helena Hentola. *Corporate Communications and Information Resources*. M.Sc. (Econ., International Business). With Biohit since 1995. Received the M.Sc. from the Helsinki School of Economics (HSE) in 1992. Studied at the Monterey Institute of International Studies (U.S.). in 1992. Additional studies at HSE and the University of Helsinki. Acted as Project Coordinator of Finland's International Business Operations (FIBO) -Research Program at HSE in 1995, as Research Associate and additional lecturer at the Department of International Business at HSE between 1994-1995 and as Researcher of the FIBO-Program between 1991-1994.

Kalle Härkönen. *Production*. M.Sc. With Biohit since 2001. Received the M.Sc. from the University of Helsinki in 1999. Acted as Factory Manager at Delipap Oy in 2001. Worked in several positions at the packaging factory Tetra Pak Oy between 1996-2000, latest as Production Manager.

Semi Korpela. *Accounting and Finance*. M.Sc (Econ.). With Biohit since 2003. Graduated from the University of Jyväskylä in 1996. Has studied also at the universities of Tampere, Helsinki and Universitat Autónoma de Barcelona and Universidad de Valladolid. During 1997-2003 worked at the Sonera Corporation in various duties related to financial issues, latest as International Business Controller.

Sari Mannonen (née Ylätupa). *Sales and Marketing*. Ph.D., (Biochemistry). With Biohit since 1995. Received the M.Sc. in 1990 and Ph.D. in 1996 from the University of Helsinki. Completed the Business Unit Management Program at the JOKO Executive Education Oy organized by the Helsinki School of Economics in 2002. Took a course in Good Laboratory Practise (GLP) in the Netherlands in 1990. Acted as biochemist and Product and Marketing Manager at Locus genex Oy between 1989-1995, in duties related to the development of diagnostic tests at Labsystems Oy between 1987-1988 and as assistant and teacher at the Dept. of Biology at the University of Helsinki between 1987-1988.

Seppo Riikonen. *Quality Systems*. Measurement and Adjustment Technician. With Biohit since 1989. Completed the Helsinki Institute of Technology in 1982. Received the Diploma in Marketing from the Institute of Marketing, Helsinki in 1992. Acted as Service Manager at Nordion Instruments Oy Ltd between 1985-1989, as Service Technician at Oriola Oy between 1984-1985, and as Project Technician at Orion Analytica Oy between 1982-1984.

Seppo Sirviö. *Information Technology*. B.Sc. (Information Technology) from the University of Kuopio. With Biohit since 2002. Acted e.g., as Manager, Customer Support, at Novo Group Plc. between 2000-2001, and as Systems Manager at Neste Chemicals Ltd. (currently Dynea Ltd.) between 1995-2000. Holds experience also on business-to-business e-business systems.

Erkki Vesanen. *Research and Development*. M.Sc. (Engineering, Electronics). With Biohit since 1989. Acted as Managing Director of Innomedia between 1986-1989. In 1976-1986 acted at Labsystems Oy in several duties related to product development, production, marketing and international operations.

MANAGING DIRECTORS OF SUBSIDIARIES

China: Esko Tikkanen. Managing Director of Finland Biohit Co., Ltd. Shanghai Representative Office since 2003.

France: Régis Carnis. Managing Director of Biohit S.A. since 1991.

Germany: Uwe Thoenges. Managing Director of Biohit Deutschland GmbH since 2003.

Great Britain: Richard Vaughton. Managing Director of Biohit Ltd. since 1992.

Italy: Enrico Marzi. Managing Director of Biohit s.r.l. between 1992-2003.

Japan: Takao Saito. Managing Director of Biohit Japan Co., Ltd. since 1998.

Russia: Victor Peppi. Managing Director of Biohit OOO since 2001.

U.S: Robert P. Gearty. Managing Director of Biohit Inc. since 2000.

SCIENTIFIC ADVISORS

Herman Adlercreutz, *M.D., Ph.D.*, Professor (emer.) of Clinical Chemistry at the University of Helsinki. Director of Folkhälsan Research Center and Head of the Institute for Preventive Medicine, Nutrition and Cancer. At Biohit advisor for diagnostics and laboratory instrumentation. Current focus on the development of test kits for phytoestrogens.

Hannu Harjunmaa, *Ph.D., Principal Scientist*, VivaScan Corporation, Massachusetts, U.S. At Biohit advisor for liquid handling and laboratory instruments. Current focus on the research and development of new techniques for liquid handling.

Matti Härkönen, *M.D., Ph.D.*, Professor (emer.) of Clinical Chemistry at the University of Helsinki. At Biohit advisor for diagnostics and laboratory instrumentation including liquid handling. Current focus on the GastroPanel.

Frank Laxén, *M.D., Ph.D., Consultant Gastroenterologist*, Department of Medicine, University of Turku, has actively studied the screening and endoscopic detection of gastric precanceroses and early gastric cancer since 1978. At Biohit advisor for diagnostics.

Aavo Mikelsaar, *M.D., Ph.D.,* Professor at the University of Tartu, Estonia in the field of human biology and genetics. Director of the Institute of General and Molecular Pathology, Medical Faculty. At Biohit advisor for cancer diagnostics.

Arto Orpana, *Ph.D.,* Docent in biochemistry at the University of Helsinki. A clinical biochemist with a background of over 10 years in basic scientific research. At Biohit advisor for diagnostics and instruments (PCR- and liquid handling equipment) and development of PCR- and other applications.

Aarno Palotie, *M.D., Ph.D., Professor,* University of California Los Angeles, Dept. of Pathology and Laboratory Medicine. At Biohit advisor for genetic laboratory diagnostics.

Ari Ristimäki, *M.D., Ph.D., Docent of Cell Biology*, is actively engaged in basic science research (molecular cell biology) at the University of Helsinki and the Helsinki University Central Hospital. At Biohit advisor for diagnostics. Current focus on cyclooxygenase-2, basic research and general applications.

Eeva-Marjatta Salonen, *Ph.D., docent*. Helsinki University Central Hospital Laboratories, Division of Virology. At Biohit advisor for diagnostics. Current focus on telomere research.

Nils-Erik Saris, *Ph.D. 1964, M.D. h.c. 1990,* Professor (emer.), University of Helsinki. Actively engaged in basic scientific research (biochemistry, biophysics, clinical chemistry). At Biohit advisor for laboratory instruments including liquid handling.

Seppo Sarna, *Ph.D.,* Professor of Biometrics at the University of Helsinki. At Biohit advisor for biostatistics and epidemiology.

Pentti Sipponen, *M.D., Ph.D., Professor*, is the Director of the department of pathology at HUS Lab (Central Laboratory of the Districts of Helsinki and Uusimaa). At Biohit advisor for diagnostics and diagnostic devices. Current focus on the GastroPanel and lactose intolerance test.

Agu Tamm, M.D., *Dr.Med*. Professor of Laboratory Medicine, University of Tartu, Estonia. At Biohit advisor for diagnostics of dyspepsia, hypolactasia and GastroPanel.

CORPORATE GOVERNANCE

Biohit Oyj adheres to the application guideline on the administration of public listed companies issued by the Central Chamber of Commerce of Finland and the Confederation of Finnish Industry and Employers (1997). Moreover, the Board of Directors has ratified a written corporate governance guideline in which the duties and areas of responsibility of the different governance bodies are defined.

The Board of Directors and the President & Chief Executive Officer (CEO) are responsible for the management of the company. The Managing Directors of the subsidiaries and the members of the Management Team assist and support the President & CEO in the management of the company.

GOVERNANCE BODIES

Board of Directors

The Board of Directors, which comprises 3-6 members elected by the Annual General Meeting (AGM), are responsible for the administration of the company and its appropriate organization. The Board elects a chairman among its members. The AGM elects the members of the Board of Directors for one year at a time and simultaneously decides on their remuneration.

In addition to the duties stipulated by law, the Board ratifies the operating principles, the busines plan and the budget of the Group. Moreover, the Board decides on the possible redirection of operations, organization structure, investments and other significant matters.

The Board decides on the internal division of its duties so that the expertise and experience of the Board members can be benefited from in an optimal way. Information on the Board members, their share ownership and division of duties is given on pages 45-46.

The Board convened 12 times during 2003.

The total remuneration for the members of the Board totalled EUR 64,140,00.

President and Chief Executive Officer

The President and CEO, appointed by the Board of Directors, is responsible for the daily management of the Group. It is the duty of the President & CEO to manage the operative activities, realization of the budget and to inform the Board of matters related with business operations and administration. The President & CEO reports to the Board of matters pertaining to the business areas and changes taken place monthly and of significant changes immediately. The Board of Directors approves the annual salary and other terms of the President & CEO.

Management Team

The Management Team comprises the President & CEO and the directors of different functions.

Information on the members of the Management Team and the division of duties is given on pages 46-48.

The President & CEO appoints the members of the Management Team and approves the terms of employment in accordance with instructions given by the Board of Directors.

The duty of the Management Team is to assist and support the President & CEO in managing the business areas and administration, and in realizing the budget.

Managing Directors of Subsidiaries

The Managing Directors of subsidiaries and the Boards of Director of the subsidiaries are responsible for the daily management of the subsidiary activities. The Managing Directors of subsidiaries operate under the management and control of the President & CEO and the Director of Administration. The Boards of Director of the subsidiaries are composed of the Managing Director and a necessary number of the members of the Management Team.

The Managing Directors of subsidiaries are responsible for ensuring that the business operations are managed and developed in accordance with the operating principles of the Group.

The President & CEO approves the salaries of the Managing Directors of subsidiaries in accordance with instructions given by the Board of Directors.

Information on the Managing Directors of subsidiaries is given on page 48.

Insiders

Biohit Oyj applies the Guidelines for Insiders approved by the Helsinki Exchanges on October 28, 1999.

Biohit's permanent insiders comprise the members of the Board of Directors, the President & CEO and the members of the Management Team.

Control System

The Board of Directors is responsible for ensuring that accounting and the control of the financial matters of the company are properly managed. The President & CEO is responsible for the operational management of book keeping and financial control.

The President & CEO and Director of Administration are responsible for the operational management of the subsidiaries of Biohit Oyj.

The auditor elected by the AGM is responsible for the audit stipulated by law. In 2003 Pricewaterhouse-Coopers Oy (Authorized Public Accountants) acted as the auditor of the Biohit Group with Hannele Selesvuo, APA, as the principal auditor. In connection with the publication of the financial statements the auditors issue their statutory report to the shareholders. The auditors report to the Board of Directors and the President & CEO.

MAJOR EVENTS IN BIOHIT'S HISTORY

Year	Events	Net sales EUR 1 000
1988	– Establishment of Biohit Oy – Basic research and market surveys – Electonic pipettor development	
1989	– TEKES[90] funding received for the development of electronic and mechanical pipettors, pipettor tips as well as microplates – Establishment of Locus genex Oy, the current diagnostics division of the Biohit Group	125
1990	– Worldwide introduction of the electronic pipettor – Assembling of pipettors and injection moulding begins in Kajaani, Finland – Introduction of the first monoclonal antibodies	491
1991	– TEKES[90] funding for the development of mechanical pipettors – First deliveries of electronic pipettors – Establishment of the first subsidiary in France – Introduction of new monoclonal antibodies	2 143
1992	– Launch of the mechanical pipettor – Launch of the multichannel electronic pipettor – Establishment of subsidiaries in Italy and the U.K. – Ph.D. Thesis of Tapani Tiusanen: An application invention of vertical measurement; the self-correcting, multiparameter measuring instrument	4 244
1993	– Launch of the multichannel mechanical pipettor – Co-operation with Eppendorf and bioMérieux begins	6 419
1994	– Development of the renewed electronic pipettor – Co-operation with Ortho Diagnostic Systems of Johnson & Johnson begins – Establishment of joint venture in Japan – Ph.D. Thesis of Osmo Suovaniemi: The vertical measurement invention, its applications and the invention of electronic liquid handling devices	8 425
1995	– Launch of several new liquid handling products – Establishment of subsidiary in Germany – Co-operation with Eastman Kodak Co. Clinical Diagnostic Systems, later acquired by Johnson & Johnson, begins	10 550
1996	– Reinforcement of international sales and marketing – Improvement of the cost structure and quality of products – The GastroPanel program begins – Ph.D. Thesis of Sari Ylätupa: An application invention of vertical measurement and immunoassays; the determination of cFn from blood samples and its importance in cancer diagnostics	12 638
1997	– Moving into new facilities in Helsinki – ISO 9001 -quality system certification – Co-operation with Becton Dickinson and 3M begins – Receiving EUREKA[91] status on the basis of which TEKES funding received for the GastroPanel -program	14 481

90 TEKES = National Technology Agency of Finland.
91 EUREKA = Europe-Wide Network for Industrial R & D. A framework through which industry and research institutes from 26 European countries and the European Union develop and exploit the technologies crucial to global competitiveness and better quality of life.

Year	Events	Net sales EUR 1 000
1998	– Assembling of pipettors and injection moulding begins in Helsinki – Locus genex Oy and Biohit Systems, Inc. become Biohit Group companies – External evaluation of the first test kit (Pepsinogen I) of the GastroPanel program – Ph.D. Thesis of Auli Linnala: Basic research on Biohit's monoclonal antibodies (cFn and tenascin), which are related with cancer diagnostics	16 881
1999	– Listing on the New Market -list of the Helsinki Exchanges – Continuation of aggressive patenting policy	20 551
2000	– Completion of new production premises in Kajaani – Accreditation of the calibration laboratory for liquid handling products – Preparation to commence the global marketing and sales of diagnostic tests and analyzing systems – Commencement of the sales of instruments – Reinforcement of international collaboration and customer service organization through acquisitions in the U.S. and Russia	24 247
2001	– Clinical evaluations carried out in various countries for assessing the reliability of the following diagnostic tests: GastroPanel for diagnosing *Helicobacter pylori* -infection and atrophic gastritis, as well as for screening the risk of gastric cancer and peptic ulcer from blood samples, and tests for diagnosing SLE and lactose intolerance. – Marketing of the GastroPanel begins for research use – Development of test kit for cellular fibronectin (cFn) – Completion of new production premises for diagnostics in Helsinki – Establishment of service laboratory	25 545
2002	– Launch of the new mLINE mechanical pipettor range – Enlargement of the electronic eLINE pipettor product range – Continuation of the automatization at the production premises in Kajaani	25 354
2003	– Launch of the multichannel versions of the electronic eLINE -pipettor range – Establishment of Biohit representative office in China – Further development of the GastroPanel and the test for diagnosing lactose intolerance – Further development of the production at the Kajaani plant	26 259

NOTES

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