

## CHAPTER 8

### STIMULATING ENTREPRENEURSHIP IN LIFE SCIENCES

*The Dutch approach*

HAIFEN HU<sup>#</sup> AND WARD MOSMULLER<sup>##</sup>

*<sup>#</sup>Director of Hyphen Project Management, former Manager Entrepreneurship of BioPartner Network, the Netherlands*

*<sup>##</sup>Director of SCILS – Science & Commerce in Life Sciences, former Managing Director of BioPartner Network, the Netherlands*

#### INTRODUCTION

Traditionally, the Netherlands has a strong science base in life sciences, particularly in biomedical and agro-food life sciences. However, the number of life-sciences researchers starting new companies trailed behind that in neighbouring countries (Ministry of Economic Affairs 1999). An analysis carried out in 1998 concluded that the main bottlenecks of the Dutch bio-business were:

- Dutch knowledge institutes lacked a business culture
- The results of scientific research were seldom commercialized
- There was not enough venture capital available for new life-sciences companies
- There was a shortage of facilities, such as office and lab space
- There were too few managers who can act as coach and mentor.

In 1999, the Dutch Ministry of Economic Affairs proposed a strategy for boosting entrepreneurship in life sciences; it launched the ‘Action Plan Life Sciences 2000-2004; breaking away from the pack’ (Ministry of Economic Affairs 1999). As a result the BioPartner programme was started in 2000, with the objectives to contribute to a more entrepreneurial culture at the Dutch academia and to assist in the generation of 75 new dedicated life-sciences companies between 2000 and 2004.

BioPartner, the practical result of this Action Plan, has been without doubt the most important initiative in the Netherlands in recent years to stimulate bio-

entrepreneurship. The Dutch Ministry of Economic Affairs allocated €45 million for this Action Plan in order to encourage the growth of the life-sciences sector. BioPartner aimed to stimulate entrepreneurship in the life sciences in the Netherlands by improving the entrepreneurial climate for bio-starters and bio-business, and by removing identified obstacles to bio-entrepreneurs' success, such as lack of information, financing, facilities and lab space during the three phases of entrepreneurship ('seed', 'start' and 'solo'). This initiative was expected to contribute to and result in the creation of 75 new dedicated life-sciences start-ups in the period 2000-2004. For this purpose the government invested €45 million in five programme instruments:

- BioPartner First Stage Grant – pre-seed fund (€11 million)
- BioPartner Facilities Support – facility fund (€5 million)
- BioPartner Start-up Ventures – seed fund (€11 million )
- BioPartner Centers – incubators (€11 million)
- BioPartner Network – information, scouting & support (€7 million).

One of the main tasks of BioPartner Network was to monitor the progress of the BioPartner programme and the status of the Dutch life-sciences sector. To this end, BioPartner Network conducted annual surveys amongst dedicated life-sciences companies in the Netherlands. This article reports on and evaluates the results of the BioPartner programme. Additionally, it also gives an overview of where the Dutch life-sciences sector stands by the end of 2004. It is divided into two sections: section A reports on the results of the BioPartner programme and section B reports on the results of the 2004 BioPartner survey.

## METHODOLOGY

### *The annual survey*

During 2000-2004 BioPartner sent out annual surveys to all identified dedicated life-sciences companies in the Netherlands. The questionnaire comprised more than 50 questions distributed over six major subjects: company data, founder's data, financial and funding data, competition, partnerships and spin-off data. The analyses and findings in this article are based on data collected from the 2004 survey. A total of 173 companies received this survey. This list of dedicated life-sciences companies was compiled using results of the previous surveys and was corroborated and replenished using records from BioPartner, Senter and the Dutch Ministry of Economic Affairs. In 6 cases, a closer examination of the business activities revealed that a particular company was not, in fact, a dedicated life-sciences company according to the definition used here, or the companies were founded after 2004. These companies were excluded from further analyses. In total, 105 companies returned the survey and an additional 27 companies were interviewed by telephone, resulting in an overall response rate of 84%. Every effort was made to ensure that the final set of survey data reflected the inclusion of dedicated life-sciences companies. However, not all questions were answered by all respondents; thus, response rates can differ per question. The relevant number of respondents and

the corresponding response rate are provided in the text or in the subscript of the corresponding figure or table. Questions regarding turnover, net result, and research and development (R&D) expenses, were multiple-choice questions: respondents were requested to indicate levels by selecting one of a set of possible ranges. In questions related to turnover, the companies could choose from the following options: 0; 1-50k; 50-200k; 200-500k; 500k-1M; 1-2M; 2-4M; 4-10M; >10M (euros). The respondents that selected >10M euros were called afterwards and requested to disclose the exact amount. All but one respondent were willing to cooperate in this way. In further calculations and analyses, we used the exact amounts in case these were disclosed, and the medians of the categories in other cases.

#### *Definition of life sciences*

Within the context of this survey, life sciences are defined as “multi-disciplinary science in which research is conducted at the building blocks and the life processes of plants, micro-organisms, animals and humans”. Within the life sciences, existing technological fields as biotechnology, pharmacology, biology, chemistry, physics and informatics are integrated. The purpose of life sciences is to utilize these technologies in order to contribute to the discovery and development of new medicines, improved treatments of diseases (human healthcare), a cleaner industry and environment, improved enzymes and new functional foods, etc. This definition of life sciences is based on the definition used by the Dutch Ministry of Economic Affairs within the scope of the Action Plan Life Sciences 2000-2004. Life-sciences companies are defined in this study as: “Those companies that apply the possibilities of organisms, cell cultures, parts of cells or parts of organisms, in an innovative way for the purpose of industrial production. They may also supply related services, and hardware and software”. Existing technological fields, including biotechnology, pharmacology, biology, chemistry, physics and informatics, are integrated into this definition. The purpose of life sciences is to utilize these technologies in order to contribute to new medicines, improved treatments of diseases, a cleaner industry and environment, improved enzymes and new functional foods, etc.

Various subdivisions of life sciences can be found. As life sciences are composed of a set of enabling technologies and disciplines that can be applied in different fields, the subdivisions used in this report are based on the field of application:

#### *Agro-food*

- Animal health – companies that use insights from the life sciences for the improvement of health of agricultural livestock
- Animal feed – companies that use insights from the life sciences for the improvement of nutrition for agricultural livestock
- Plants and seeds – companies that focus on enhancement of the quality or the characteristics of plants
- Food/nutraceuticals – companies that aim at improving the quality of foods and developing new functional foods.

#### Human health

- Diagnostics – companies that develop tools for identifying human or animal diseases, e.g. different types of antibodies, genetic diagnostics that use polymerase chain reaction (PCR) technology or other molecular-biology techniques
- Therapeutics – companies that produce biotechnology-derived products developed to improve the treatment of human diseases, e.g. biopharmaceuticals and gene therapy
- Prevention, e.g., vaccines.

#### General biotechnology

- Bio-chemicals, e.g. enzymes
- Equipment, instrument and reagents – companies that develop, produce and sell instruments, laboratory equipment, reagents and kits for the life-sciences industry.

#### *Dedicated life-sciences companies*

This article focuses solely on dedicated life-sciences companies in the Netherlands. Dedicated life-sciences companies (Allansdottir et al. 2002), such as Crucell, Keygene and OctoPlus, have life sciences as their core activity and spend a large part of their R&D budget on them. The criteria for inclusion are the following:

- The firm is located in the Netherlands
- The firm is registered with the Dutch Chamber of Commerce
- The firm is an independent entity (this excludes business units and subsidiaries of existing companies or public research institutes)
- The firm has R&D activities in one or more of the major areas that constitute the domain of the Life Sciences.

Companies were not selected for review in this report if they fulfilled one of the following criteria:

- Diversified life-sciences companies – companies that are actively involved in life-sciences R&D, though their core business is not in life sciences, such as DSM, Unilever and Akzo Nobel
- Classical life-sciences companies – companies that use only classical biotechnological techniques, such as traditional plant-breeding companies
- Foreign companies with only a subsidiary in the Netherlands – dedicated life-sciences companies of foreign origin, that have set up a Dutch subsidiary, such as Amgen, GenMab, Genentech, Centocor and Biogen
- Support companies, service providers, such as investors, consultants, legal services and start-up support organizations
- Research institutes, such as Netherlands Vaccine Institute and Plant Research International.

## BIOPARTNER AND ITS ACHIEVEMENTS

In this section, we introduce the different BioPartner instruments and list their results. The data in this chapter were provided by the managers of the different instruments.

### *BioPartner First-Stage Grant / STIGON*

BioPartner First-Stage Grant (FSG) aimed at stimulating researchers to translate their scientific knowledge and results into a feasible business plan. In December 2003, BioPartner FSG merged with STIGON, a similar programme that focuses on innovative projects in the pharmaceutical field. The Netherlands Organisation for Scientific Research (NWO) and the Netherlands Organisation for Health Research and Development (ZonMw) added €2 million to the fund. FSG/STIGON provided grants for researchers to translate their scientific knowledge and results into a feasible business plan. The grant, a maximum of €250,000 for a maximum period of two and a half years, paid for researcher salaries and technical assistance, materials, expenses for external advice, training and coaching. In this ‘first stage’, both technical and economical feasibility should be assessed, resulting in a viable business plan. The researcher should be employed by the research organization that carries out the project. An external and independent advisory board reviews the proposals. BioPartner First-Stage Grant/STIGON was managed by NWO and ZonMw.

### *Result*

In the period of 2001 – (February) 2005 a total number of 133 applications were received. More than half (69) of the applicants received subsidy. By February 2005 this had resulted in the completion of 33 FSG projects, 24 feasible business plans and the creation of 13 new start-up companies. Seven projects were still in the pursuit of finding additional funding and four projects were discontinued. It is expected that the number of companies will increase significantly over the next few years when projects that have recently been completed will be successful in finding investors, and projects that are currently still running will be completed.

Before the merger with BioPartner First Stage Grant, STIGON funded 18 projects. These projects have all been completed and led to the founding of 9 start-up companies, the majority of which are pursuing start-up financing and are actively partnering with other companies in order to quicken the time-to-market.

### *BioPartner Facilities Support*

BioPartner Facilities Support (BFS) provided loans for pre-financing (expensive) life-sciences facilities. It enabled start-ups to use innovative and advanced equipment and R&D facilities in collaboration with universities or research organizations. This arrangement was known as Facility Sharing (FS). The university or research organization must apply for funding in cooperation with the start-up and

part of the cost must be recouped within five years through earnings from contract research. In 2003, a new programme, Facility Leasing (FL), was launched as an alternative to FS. FL arrangements provided start-up companies the opportunity to lease advanced facilities independent of collaboration with universities or research organizations. BFS was managed by *mibiton*. The fund was closed as of 1 January 2005.

#### *Result*

During its life-span, BFS received a total of 63 applications for pre-financing facilities. Nineteen of these proposals were approved, of which 12 were for FS and 7 for FL. A nice example of a facility that was co-financed is the 'CombiChem Synthesestraat', a modular automated facility for performing parallel synthesis, stationed at the Radboud University Nijmegen and used by the company Chiralix.

#### *BioPartner Start-up Ventures*

BioPartner Start-up Ventures (SuV) is a public venture fund for life-sciences start-ups. SuV invested up to a maximum of € 227,000 in life-sciences start-up companies. BioPartner SuV was able to invest an additional € 227,000 in a subsequent financing round. An important condition for an investment was matching funding from other (private) investors. Investments were provided in exchange for shares in the start-up company or as a combination of shares and a convertible loan. BioPartner SuV was managed by Zernike Group B.V.

#### *Result*

In the period of 2001-2004, BioPartner SuV received 224 proposals and approved 68 of them. More than half of these proposals (38) succeeded in finding co-financing and resulted in SuV participation. By the end of 2004 another 30 start-ups were in the pipeline to find co-investment and become SuV participants.

#### *BioPartner Centers*

The BioPartner Centers offer suitable housing and services for life-sciences start-up companies. The Centers have complete infrastructures including office space, laboratories, R&D, pilot-plant facilities and shared services. The Centers give start-ups easy access to the network and facilities of local universities, research organizations and other companies operating in the local science park. Overall, BioPartner Centers play an active role in facilitating start-ups in their region. In total, there are six BioPartner Centers. They are located in Amsterdam, Groningen, Leiden, Maastricht, Utrecht and Wageningen. The BioPartner Centers will continue to operate under the BioPartner banner after 2004.

#### *Result*

By the end of 2004, a total of 88 companies had located themselves in the various

BioPartner Centers. About 70% of these tenants are life-sciences start-up companies, such as Prosensa, Pharmacell and Catchmabs.

#### *BioPartner Network*

BioPartner Network (BPN) focused on facilitating and stimulating entrepreneurship through advice, information, support, training programmes, and creating and expanding networks. BPN assisted in identifying those ideas suitable for transformation into a life-sciences business through its network of scouts, who are responsible for identifying emerging enterprises at the Dutch universities. Furthermore, BPN's tasks included monitoring the progress and consistency of the BioPartner programme. This part of the BioPartner programme concluded its activities at the end of 2004.

#### *Result*

Since its establishment, BPN has organized various national and international conferences, seminars, workshops and meetings. BPN has conducted four Masterclasses Biobusiness. BPN also initiated two BioPartner chairs at two universities to promote entrepreneurial culture. In order to track and trace business ideas and entrepreneurial researchers at Dutch universities BPN appointed several scouts. Also, BPN produced several publications: e.g., information modules on finance, Intellectual Property Rights, Human Resource Management and business development, a guide for entrepreneurial scientists and five sector reports on the life sciences. Due to its in-depth knowledge of the Dutch life-sciences sector, BioPartner Network frequently acted as the spokesperson for new and young life-sciences companies in the Netherlands.

BioPartner Network concluded its activities in December 2004. Several products and services of BioPartner found their way to the market. The BioPartner Masterclass Biobusiness is now being exploited jointly by Wageningen Business School and Rotterdam School of Management. The two BioPartner chairs are taken over by the universities, and a network for education in the field of entrepreneurship in the life sciences has been created.

When it comes to promotion of entrepreneurship in general, the new organization TechnoPartner (Ministry of Economic Affairs 2004) has assumed the torch. This organization will also keep the BioPartner website and diverse publications online.

### RESULTS OF ANNUAL SURVEY OF DEDICATED LIFE-SCIENCES COMPANIES 2004

This section of the report describes the findings of BioPartner's 2004 survey of dedicated life-sciences companies in the Netherlands. It provides analyses and insights into Dutch bio-entrepreneurial activities and overviews of numbers, performance, dynamics and features of these companies, their founders, their strategies and their future expectations.

*Table 1. Key BioPartner highlights, 2000 - 2004*

<b>Year</b>	<b>Defining event</b>
2000	Launch of Life Sciences Action Plan 2000-2004: breaking away from the pack
2000	Launch of the BioPartner programme
2000	25 new life-sciences companies established
2001	22 new life-sciences companies established
2002	19 new life-sciences companies established
2002	Eric Claassen en Hans Dons appointed as BioPartner professors Entrepreneurship in the Life Sciences
2003	21 new life-sciences companies established
2003	BioPartner milestone reached: 75 new life-sciences companies created since 2000
2004	Launch of the Technopartner programme
2004	Launch of Action Plan Life Sciences: seizing opportunities, dealing with obstacles
2004	First successful exit of BioPartner Start-up Ventures realized (CatchMabs)
2004	22 new life-sciences companies established
2004	BioPartner Network terminated

*Highlights of the Dutch life-sciences sector 2000-2004*

The Dutch Ministry of Economic Affairs created BioPartner with the objective to increase the number of start-up companies substantially, by 15 a year in the period 2000-2004. In the subsequent years, the number of new start-ups increased by an average of 22 a year, surpassing the initial goals. At the end of 2004, the Netherlands is home to 157 of those companies, many of which are university spin-offs. The shortage of lab and office space diminished with the establishment of six new life-sciences incubators (BioPartner Centers). In the following table, the key BioPartner highlights during 2000-2004 are depicted.

*The year 2004 in review*

In 2004, the Dutch economy showed signs of moderate recovery; the economy grew by 1.3%, the number of start-ups increased, and the confidence of entrepreneurs rebounded. At the same time, the decrease in employment was the largest in the past 20 years (CBS 2005a). In a year when the economy was mixed, the Dutch life-sciences sector nonetheless continued to grow progressively. The sector demonstrated an increased number of companies, increased employment, and increased turnover and R&D expenditure.

*Development of companies**Entrants*

In 2004, the Netherlands gave rise to 22 new dedicated life-sciences companies.



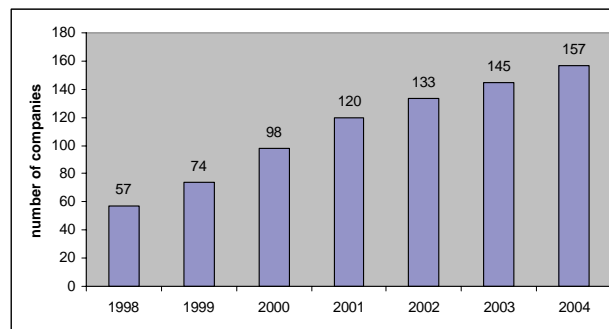
More than half of these new entrants were spun out from universities ('university spin-offs') and corporate firms ('company spin-offs'): 13 and 2, respectively. This is an indication that the recent BioPartner investments – primarily focused on commercializing academic research – were starting to bear fruits.

#### *Exit, mergers and acquisitions*

In 2004, the number of exits in the Dutch life sciences stabilized and was more or less comparable to that in 2003; 6 dedicated life-sciences companies went out of business in the Netherlands: Arrante Biosciences, Bioscan, Cryptogen, Gendomed, Merska and Schelpdier Ponton Kweek. One company relocated its activities abroad (Isotis), and 3 companies were acquired; Chromagenics by Crucell, Microscreen by Ribo Technologies BV, and Halotech by the Priva Groep.

#### *Total number of dedicated life-sciences companies*

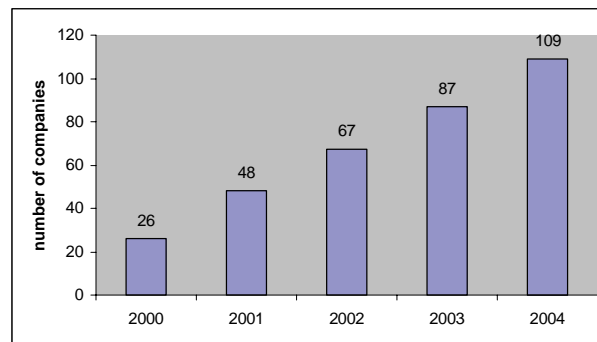
Taking the numbers of entrants, exits, and mergers and acquisitions (M&A) into consideration, the net result in 2004 was an increase of 12 companies. By the end of 2004, the Netherlands encompassed 157 dedicated life-sciences companies. Compared to the preceding year, the total number of companies grew by 8% in 2004. This demonstrates that there is a continuous growth rate in Dutch life-sciences despite difficulties in the financial markets. Figure 1a shows that, despite a number of bankruptcies and M&A, the Dutch life-sciences sector grew considerably between 1999 and 2004, with a net increase of 83 companies. Before the foundation of BioPartner, the founding rate of new start-up companies for several years balanced between 4 and 6 companies a year. BioPartner had the objective to increase the number of start-up companies substantially by at least 15 a year or a total of 75 in the period 2000-2004.



**Figure 1a.** Yearly population of dedicated life-sciences companies since 1998

Despite impeding macroeconomic factors and volatile financial markets, 109 new life-sciences companies were established in the Netherlands in 2000-2004, an average of 22 companies a year (Figure 1b). One can say that BioPartner has contributed to a change of the climate in the Netherlands towards a more

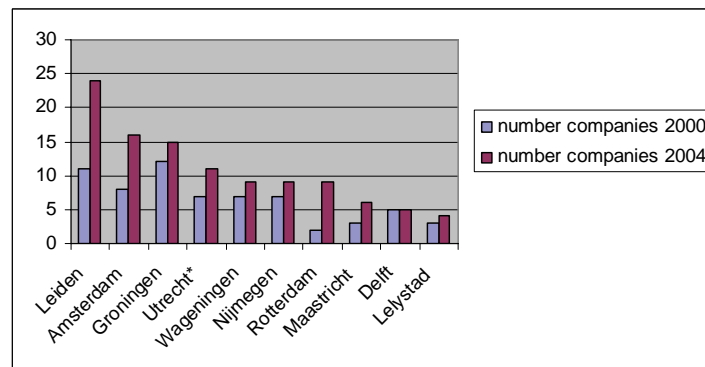
entrepreneurial attitude. Knowledge of Dutch research institutes is currently more often commercialized than in previous years. Of these 109 companies, 9 companies folded, 8 were merged or were acquired, and 92 companies are still in business. A list of the 109 dedicated life-sciences companies established since the launch of BioPartner in 2000 and their current status can be found in Appendix 1.



**Figure 1b.** Number of dedicated life-sciences companies established since the launch of BioPartner in 2000 (cumulative)

#### Regional distribution

Figure 2 illustrates the geographic distribution of dedicated life-sciences companies in the 10 main cities with life-sciences activities. The figure shows the number of companies in these regions in 2000 and in 2004. Between 2000 and 2004, in 9 out of 10 regions the population of life-sciences companies grew, but no significant shifts have occurred between cities. For several years now, Leiden has been and continues to be the leading region for the life sciences.



**Figure 2.** Regional distribution of dedicated life-sciences companies in 2000 compared to 2004 (\*including Bilthoven)



Figure 3. The Dutch life-sciences sector map

### *The Dutch life-sciences sector mapped*

The map in Figure 3 illustrates the location and intensity of Life Sciences activity in the Netherlands; it covers the most important Life Sciences participants and activities in the Netherlands, including: agro-food – human health – general Life Sciences companies, incubators and science parks in the Life Sciences, Genomics Centers of Excellence, and other important Life Sciences industry participants.

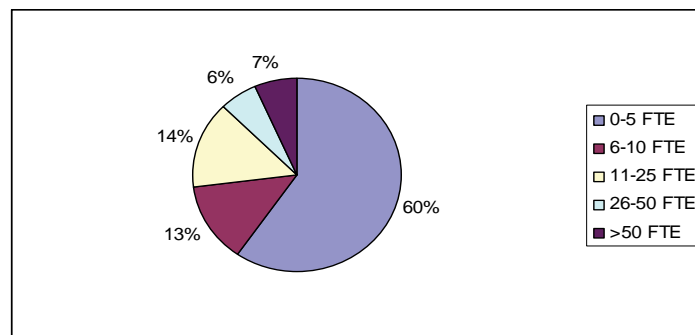
### *Employment*

While employment in the Netherlands (measured in labour years) decreased by 1.7% in 2004, the biggest decrease in employment in more than 20 years (CBS 2005b), the Dutch life-sciences sector showed moderate growth. At the end of 2004, about 2,150 Full Time Equivalents (FTEs), of which 52% are involved with R&D, were employed by dedicated life-sciences companies in the Netherlands, a moderate increase of 3% compared to 2003. This number is based on the data of 132 respondents (response rate = 84%). Compared to 2000, employee numbers have increased by 112%. The five largest dedicated life-sciences companies in terms of employment can be found in Table 2. Together, they account for more than 25% of the total workforce of the sector.

**Table 2.** *Top five largest companies in terms of employment*

1	Crucell
2	OctoPlus
3	Syncom
4	Keygene
5	Synco Bio Partners

The majority of the dedicated life-sciences companies are still small. Company sizes range from 1 to 209 FTEs. Most companies have workforces of fewer than 10 FTEs (see Figure 6).



**Figure 4.** *Percentage of dedicated life-sciences companies with, respectively, < 5, 5 to 9, 10 to 25, 26 to 50 and >50 FTEs employed; n = 104, response rate = 66%*

These small companies account for 73% of Dutch Life Sciences firms. Only 7% of companies are medium-sized, with between 51 and 200 employees. Compared to 2000, the proportion of the very small companies (less than 10 FTEs) has increased from 65% in 2000 to 73% in 2004.

#### *Financials and funding*

In this part of the chapter, we assess the financial performance of the sector by analysing the turnover, net result, R&D expenditure and funding (Table 3).

#### *Turnover*

In 2004, the combined turnover of the survey respondents approached €126 million, resulting in an extrapolated turnover of €190 million for the entire sector. The average turnover per company was €1.2 million. These figures are based on data collected from 104 companies and represent an overall response rate of 66%. Together, dedicated life-sciences companies increased their turnover by €20 million compared to 2003 – a growth of 12%.

#### *Change in turnover*

To verify the estimated turnover, we asked the respondents to indicate whether their turnover in 2004 has increased or decreased compared to 2003. Twenty-two companies reported neither an increase nor a decrease. Only 4 companies reported a decrease, whereas 56 companies reported a combined increase of €23 million.

#### *Net result*

Another performance indicator is net result. As expected considering the relatively early stage of many Dutch life-sciences companies, the business activities were associated with high initial losses. In 2004, the net result of the sector amounted to a loss of €75 million. Compared to 2003, the losses have been reduced by 3%. These figures are based on data collected from 91 companies and represent an overall response rate of 58%. Little more than a fifth of the dedicated life-sciences companies reached break-even in 2004, while 35% made a profit and 43% sustained a loss.

#### *Increased labour productivity*

In 2004, labour productivity (turnover per FTE employee) increased by 6% to €86,000 per FTE compared to the previous year. At the same time, R&D expenditure per FTE also increased by 6% to €54,000 per FTE.

#### *R&D expenses*

In 2004, dedicated life-sciences companies spent about €118 million on R&D, 9% more than in 2003. This investment represents 62% of their total turnover. To put

this number in perspective: Dutch companies have spent €4.7 billion on R&D in the Netherlands in 2001 – 1.1% of the GNP (CBS 2004).

**Table 3.** Turnover, net result, R&D expenses, labour productivity, and R&D expenditure per FTE, estimated for the dedicated life-sciences sector

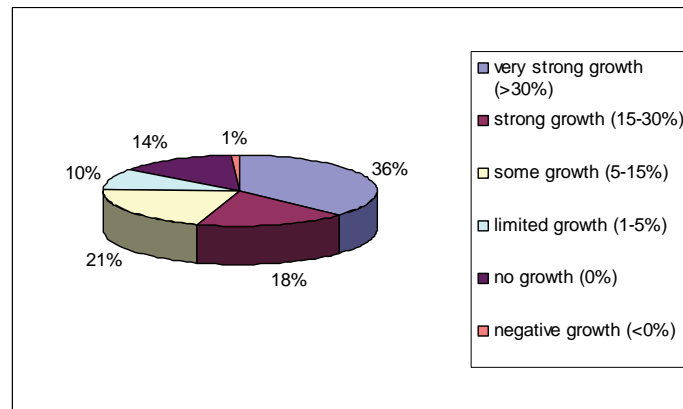
	Response rate	2004	2003	% change
Turnover*	66 %	€190 M	€170 M	12 %
Net result**	58 %	€- 75 M	€- 77 M	3 %
R&D expenses	64 %	€118 M	€108 M	9 %
Labour productivity (turnover per FTE)		€86 K	€81 K	6 %
R&D expenditure per FTE		€54 K	€51 K	6 %

\*subsidies, investments and loans not included

\*\*calculated as EBIT

#### *Outlook on financial performance*

In general, respondents are optimistic about the turnover development of their company in the coming year. Compared to 2003, however, respondents' outlook on their financial performance has deteriorated slightly. The percentage that expects their turnover to increase strongly or very strongly (15% or more) has dropped from 59% to 54% and the percentage that expects no growth for 2005 increased by 3% to 14%.

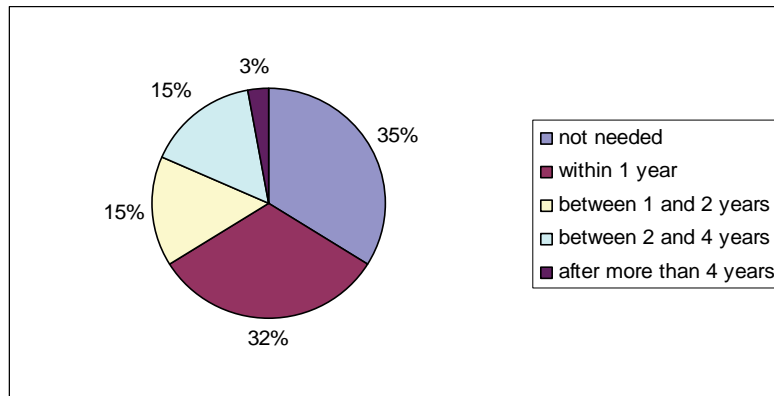


**Figure 5.** Expected turnover growth for 2005; n = 102, response rate = 65%

#### *Survival index*

To determine the viability of dedicated life-sciences companies in the Netherlands we analysed their survival index. Survival index refers to how long, in years, a company can last on its existing cash; it measures the relationship between cash on

hand and net burn rate. The results disclose that 35% have sufficient cash and do not need additional financing rounds. About a third of the respondents have less than one year's cash requirements readily available and 47% have less than 2 years cash on hand.



**Figure 6.** Percentage of companies that intend to pursue a financing round within 1 year, between 1-2 years, between 2-4 years, and after 4 year(s);  $n = 91$ , response rate = 58%

So, the survival indexes reveal that about 40% of the respondents have sufficient cash to fund 2 or more additional years of research and operations. This means that, in case the capital markets and investment behaviour fail to recover, the group of companies with a survival index of less than 2 years will need to embark on alternative activities over the next 24 months, such as significant spending reductions. Unless the companies manage to adapt quickly and come up with creative responses, many of these firms will be forced to shutdown or merge. Increased consolidation activity and shutdowns in the next few years are to be expected if the shortage of capital continues.

#### *Sources of funding*

Life-sciences companies, and particular drug development companies, require substantial amounts of funding. Access to seed capital, early and mid-stage capital is critical to the survival and success of life-sciences companies. A number of funding options exist, ranging from VC to subsidies and the public market.

#### *Venture capital and informal investors*

The year 2004 was difficult for life-sciences companies in the Netherlands to raise money from VCs and informals. And if they succeeded in securing a financing round, the amounts companies raised were generally relatively low. Among the 102 respondents, 21 companies attempted to raise money in 2004 but did not succeed. On the other hand, another 21 companies did succeed in getting their business plans

funded in 2004. We estimate, based on the responses of these companies, that about € 30 million of venture capital was invested in Dutch life-sciences companies in 2004.

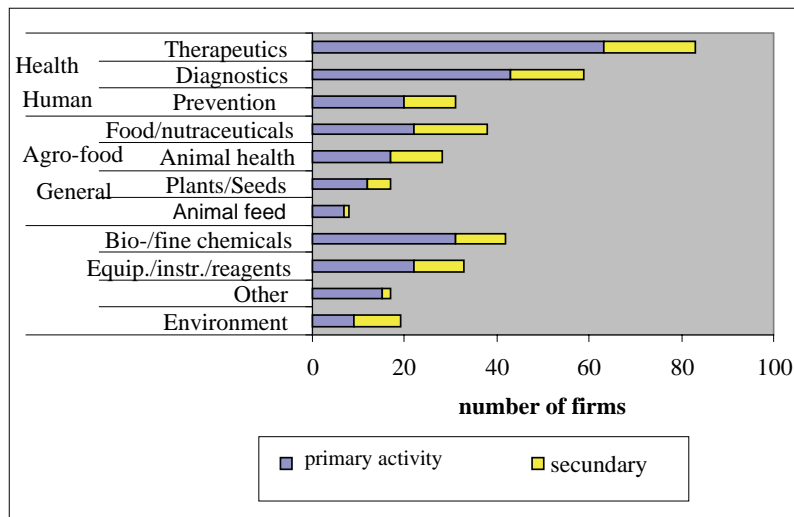
### *IPO*

While in the USA the biotech Initial Public Offering (IPO) market returned with 30 offerings and raised a total of nearly \$1.8 billion (Burrill & Company 2005), the IPO window for the Dutch biotech remained shut for the fourth consecutive year with no biotech company attempting and entering the publicly traded market since the IPOs of Crucell and IsoTis in 2000. This changed in 2005 when Galapagos Genomics entered the Euronext Stock Exchange listing, followed by the IPO of OctoPlus in 2006 and the IPO of Amsterdam Molecular Therapeutics in 2007 (the Dutch life-sciences companies Fornix Biosciences, Pharming Group and Crucell were already listed in the Euronext Eurolist).

### *Subsidies*

Dedicated life-sciences companies have come to rely even more on subsidies to finance their development trajectories in times of hesitant capital markets. On top of their turnover, the dedicated life-sciences sector had about €60 million in subsidies at their disposal in 2004. This figure is based on the response of 101 companies with an average of €380 K per company.

### *Industry characteristics*



**Figure 7.** Primary and secondary fields of applications by dedicated life-sciences companies. Note: a company can have more than one field of application

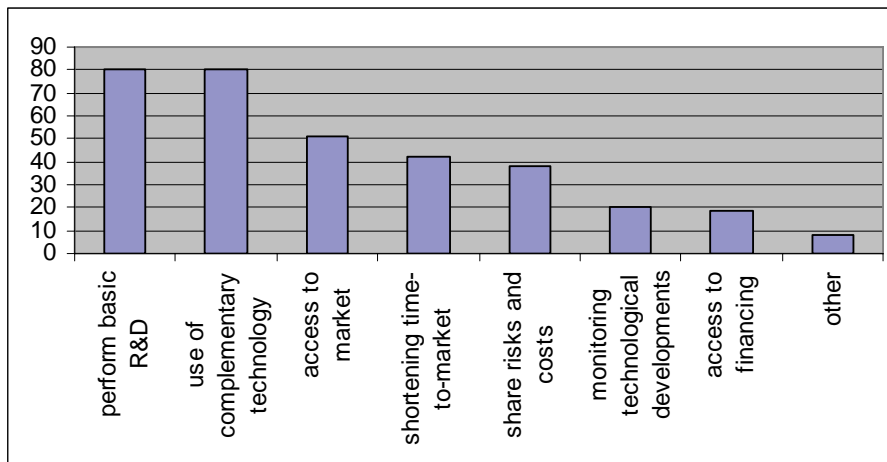


### *Field of application*

Life sciences can be divided into three sub-sectors depending on the field of application: agro-food, human health and general biotechnology. These sub-sectors can be broken-down further to 11 fields of application (see Figure 7). The respondents were asked to indicate which field of application was their primary business activity and which their secondary. The largest field of application in the Netherlands is human therapeutics. The results of our survey show that the majority of dedicated Dutch life-sciences companies are engaged in some field of human health, particularly in therapeutics and diagnostics.

### *Partnerships*

It is well-known that small biotech companies and large pharmaceutical companies tend to partner, providing the biotech companies with much needed cash and fuelling pharma with drug leads for their product pipeline. But life-sciences companies also partner to a great extent with other life-sciences companies, universities and research institutes. The reasons for partnering can be diverse and could include the following: to shorten time-to-market, to access funding, to access a market, to perform basic R&D, to spread risks and costs, to monitor technological developments, and to use complementary technology (Figure 8). Our survey results show that the two most important goals for partnering companies are performing basic R&D together and the use of complementary technology.



**Figure 8.** Reasons for partnering;  $n = 97$ , response rate = 62 %

Note: a company can have more than one reason for partnering

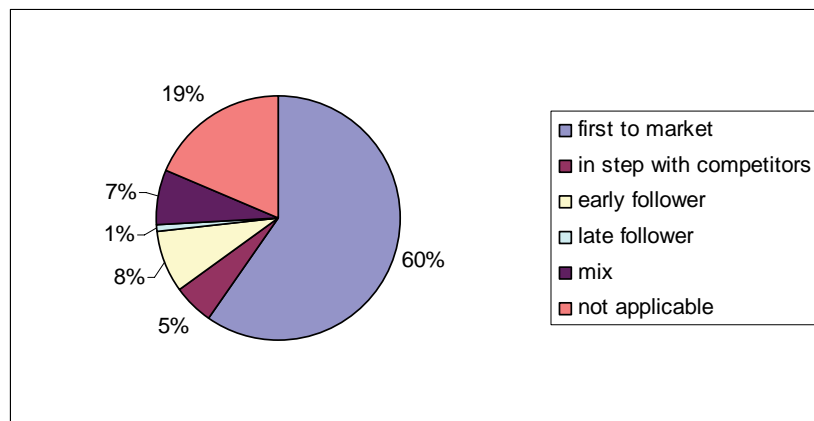
### *Patent portfolio*

Building high-value patent portfolios is critical to the success of life-sciences companies. This is particularly relevant in the current investment climate where venture capitalists (VCs) have become more selective, often insisting that the

companies have broad, patented inventions to shield their investments from competition. Dutch dedicated life-sciences companies have on average 10 patents in their portfolio and another 7 patent applications pending. It is evident that only a few companies hold the majority of the patents. These data are based on responses of 91 and 86 companies, respectively.

#### *Product portfolio*

The life-sciences sector is renowned for its complex and lengthy product development trajectories, especially when it comes to drug development. But then again, drug discovery and drug development are the core value-generating processes, with some drugs having revenues over a billion euros a year. In general, the product life cycle starts with product R&D. During this period, no revenues are generated. Once the product reaches the market, return on investment finally takes place. All new therapeutics must complete three sets of clinical trials before they can be submitted for market approval to the FDA (US Federal Drug Administration) and/or EMEA (European Medicines Agency). Long lead times exist between the identification of a promising compound and product approval and market launch. This process can take up to 8 to 14 years. Given these timeframes and the fact that the majority of the dedicated life-sciences companies in the Netherlands are less than 10 years old, it is understandable that no drug produced by a dedicated Dutch life-sciences company has been approved for the market yet. However, there is light at the end of the tunnel; several companies now have compounds in clinical development. For example, Pharming is nearing the end of the development programme for its recombinant human C1 inhibitor. The product is now in phase III of clinical testing in humans.



**Figure 9.** Dedicated life-sciences companies and their new product strategies;  $n = 97$ , response rate = 62 %

*New product strategies*

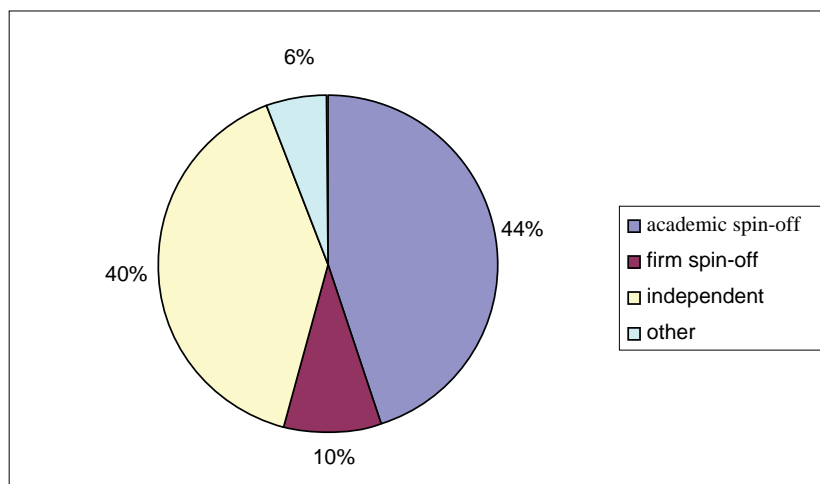
The life-sciences industry is highly innovative, driven by scientific and technological advances and cutting-edge technologies. Therefore, it is not surprising that 60% of the companies pursue a first-to-market strategy (see Figure 9). Among the other new product strategies, less frequently employed by Dutch life-sciences companies are early follower (8%), late follower (1%) and in step with competitors (5%). Seven percent adopted a mix of the fore-mentioned product strategies.

*Time to market*

More than 40% of the companies expect a new product release within the next 12 months. It is to be expected that these concern products that do not require years of clinical testing. Traditionally, the Dutch are trade- and export-minded. Furthermore, life sciences are by definition an international industry. This is reflected by the percentage of companies that act mainly globally; three quarters of the companies have a mainly global focus, whereas only 3% focus primarily on the homeland. One out of five companies considers itself to be the market leader. While in 27%, competitors are seen as market leaders. More than half of companies work in an area with no clear market leader, according to the respondents.

*Mode of founding*

Compared to 2001, the percentage of university spin-offs has increased remarkably; instead of 29% in 2001 (BioPartner 2002), university spin-offs represent 44% of all dedicated life-sciences companies at the end of 2004. Independently established companies and corporate spin-offs accounted for 40 and 10%, respectively, in 2004. Clearly, universities have a growing entrepreneurial attitude.



**Figure 10.** Dedicated life-sciences companies and mode of founding;  $n = 105$ , response rate = 67%

*Business models*

For several years we have witnessed a shift in business models. Companies have taken the ongoing difficulties in the financial markets into account and reviewed their business models and strategies. Many new companies combine some sort of short-term cash-generating activities with long-term drug discovery processes. Also, more mature companies, such as OctoPlus, have evolved from a service company to a company with a mixed business model.

**Table 4.** *Business models adopted by dedicated life-sciences companies; companies founded before 2000 compared to companies founded from 2000 – 2004; n = 107, response rate = 68%*

<b>Business model</b>	<b>Founded before 2000</b>	<b>Founded in 2000-2004</b>
Service company	33%	8%
Tool company	7%	8%
Product company	11%	27%
Hybrid company	49%	57%

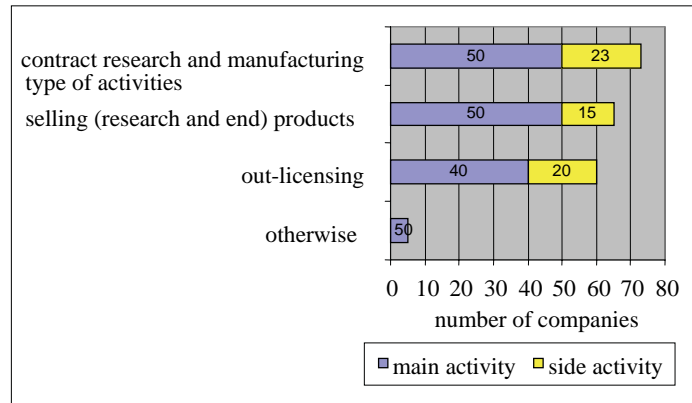
In general, there are 4 typical business models in the life sciences:

- The ‘service’ business model. These companies offer contract research or custom services. The main benefit of this model is that the firm can start generating revenue from day one
- The ‘tool’ business model. Tool companies focus on developing platform technologies. Revenues are often generated through out-licensing, milestone payments and royalties
- The ‘product’ business model. Product companies focus on developing and selling end products
- The ‘hybrid’ business model. Companies that have adopted this model combine two or more aspects of the above models.

We compared companies founded before 2000 to companies that have been established in recent years (between 2000 and 2004) in Table 4. The most striking difference is the shift from service companies in favour of the other three business models and, in particular, the product business model. While a third of the more established companies focus solely on providing services, only 8% of the newer companies have adopted this business model. More than a fourth of the companies founded between 2000 and 2004 are focusing on developing products (Figure 11).

But with more than half of the respondents adopting some sort of hybrid business model, this is by far the most dominant business approach. Many companies combine expensive product development with generating short-term income by providing services and out-licensing technologies. Despite the high risk and long development timelines, VCs tend to have a bias towards product companies, whereas ‘platform’ companies struggle to find VC funding. Among the 22 new start-ups of 2004, the hybrid-company business model is by far most frequent (10), followed by the product company (8). Despite this trend, contract research and

contract manufacturing are the two main revenue-generating activities of the sector, followed closely by selling products (see Figure 11).



**Figure 11.** Dedicated life-sciences companies by revenue-generating activities; n = 102, response rate = 65%

Note: a company can have more than one revenue generating activity

*Best dedicated life-sciences companies*

We asked the survey respondents which dedicated life-sciences companies are the five best companies in their view. This peer review resulted in the following top five (see Table 5).

**Table 5.** Top five most appealing Dutch dedicated life-sciences companies according to the respondents

- 1 Crucell
- 2 OctoPlus
- 3 Pharming
- 4 Pepscan
- 5 Galapagos

*Functional areas represented by management team*

Dedicated life-sciences companies are led by cross-functional management teams. The management teams of dedicated Dutch life-sciences companies on average consist of 2 to 3 individual members, each executive with responsibilities for separate functional areas. Our survey results show that the three predominant functional areas that are represented in the management teams are R&D, business development and finance.

The results of the survey show that although the founders of dedicated life-sciences companies have relatively little work experience in areas such as finance, marketing and business development, they compensate for this in their management teams by bringing in expertise in these functional areas (see Table 6).

*Table 6. Management teams and functional areas represented*

<b>Functional area</b>	<b>Percentage represented</b>
R&D	81 %
Business development	75 %
Finance	66 %
Marketing & Sales	47 %
Productions & Operations	42 %
IP	41 %
Alliance management	28 %
Clinical development	19 %

#### DISCUSSION AND CONCLUSION

The main purpose of BioPartner was to improve the entrepreneurial climate in the life-sciences sector in the Netherlands. In order to achieve this, BioPartner needed to bring about a significant change in the attitude and culture in Dutch academia towards entrepreneurship. Since a change in culture is difficult to quantify, the number of start-ups was taken as the performance indicator for measuring the impact of the BioPartner programme. The BioPartner initiative was expected to result in the creation of 75 new dedicated life-sciences start-ups in the period 2000-2004, equal to an average of 15 new companies a year. After five years, a total of 109 new dedicated life-sciences companies were established, an average of 22 start-ups a year. A substantial increase, since in the years before only 4-6 new companies a year were started. The total budget made available for the BioPartner programme was € 45 million. Of this, € 11 million was invested in incubator (BioPartner Centers), buildings that are still in operation. Therefore, it can be concluded that, with a cash investment of €34 million, a net growth of more than 100% in the number of life-sciences companies has been realized in 5 years' time.

The Dutch life-sciences sector has thrived in recent years despite the unfavourable macroeconomic situation during this period. Between 2000 and 2004, the sector showed double- and triple-digit growth; employee numbers have more than doubled, and revenues have increased by 164%. Despite a number of shutdowns and mergers and acquisitions, the Dutch life-sciences sector is home to more than twice the number of companies compared to 5 years ago. By the end of 2004, there were 157 dedicated life-sciences companies in the Netherlands, with a workforce of 2,150 FTEs generating a combined annual turnover of €190 million. Nevertheless, it is yet uncertain whether the Netherlands will capture the full benefit of the recent developments. The Dutch life-sciences sector is still in an early stage and consists of primarily small, privately held, often loss-making, entrepreneurial

companies with fewer than 10 employees. Many of these companies are vulnerable. Only 35% of these companies are profitable, whereas many companies will need additional funding within the next few years. In the near future, a wave of BioPartner (First Stage Grant) start-ups will be ready for launch. Without additional help – in support or in cash – many of these initiatives could face severe difficulties in realizing continuity and growth. The next few years will be decisive for the Dutch life-sciences sector. In the years ahead, it is important for the Netherlands to retain and strengthen its supportive environment for new company formation.

To this end the Dutch Ministries of Economic Affairs and of Education, Culture and Science jointly have set up a new stimulation programme for entrepreneurship: TechnoPartner. This action programme aims for an improvement of the techno-starter climate in general and comprises a package of interrelated concrete actions:

- The TechnoPartner Seed Capital scheme to stimulate and mobilize the bottom end of the Dutch venture-capital market, so that techno-starters can satisfy their capital requirements in the early phase. From 2006, several new life-sciences-oriented seed funds were started
- TechnoPartner Knowledge Exploitation Subsidy Arrangement (SKE), which offers public-private consortia, consisting of one or more knowledge institutes and one or more private companies, (financial) means to professionalize utilization of scientific knowledge by spin-offs and industry
- TechnoPartner platform, which will offer information and expertise and will create an ongoing inventory and agenda of the obstacles faced by techno-starters.

At this point it is hard to determine how successful TechnoPartner will be to hold on to the momentum that was created by BioPartner. Continuation of research is necessary to come to well-grounded conclusions and to determine whether TechnoPartner's stimulation policy is adequate or needs to be adjusted to support entrepreneurship in the life sciences.

## REFERENCES

- Allansdottir, A., Bonaccorsi, A., Gambardella, A., et al., 2002. *Innovation and competitiveness in European biotechnology*. European Commission, Brussels. Enterprise Papers no. 7. [[http://ec.europa.eu/enterprise/library/enterprise-papers/pdf/enterprise\\_paper\\_07\\_2002.pdf](http://ec.europa.eu/enterprise/library/enterprise-papers/pdf/enterprise_paper_07_2002.pdf)]
- BioPartner, 2002. *The Netherlands life sciences sector report: gaining momentum*. Biopartner, Ede.
- Burrill & Company, 2005. *Quarterly reports: Biotech ends the year on a high note, January 05, 2005*. Burrill & Company, San Francisco. [[http://www.burrillandco.com/burrill/pr\\_1105471928](http://www.burrillandco.com/burrill/pr_1105471928)]
- CBS, 2004. *Knowledge and economy 2003: research and innovation in the Netherlands [Dutch]*. Statistics Netherlands, Heerlen. [<http://www.cbs.nl/NR/rdonlyres/5CB82B9D-3978-4056-A6ED-35ABE06D8C43/0/kenniseneconomie2003.pdf>]
- CBS, 2005a. *Economy grows 1.3% in 2004*. Statistics Netherlands, Voorburg. Press Release no. PB05-017. [<http://www.cbs.nl/NR/rdonlyres/7646110C-E1C4-4B5B-B38F-E220085A0F22/0/pb05e017.pdf>]
- CBS, 2005b. *More bankruptcies again*. Statistics Netherlands, Voorburg. Press Release no. PB05-011. [<http://www.cbs.nl/NR/rdonlyres/9A554253-D68B-4DAA-B14E-CE9A1CB211B8/0/pb05e011.pdf>]
- Ministry of Economic Affairs, 1999. *Life sciences action plan 2000-2004*. Ministry of Economic Affairs, The Hague. [<http://appz.ez.nl/publicaties/pdfs/25B26A.pdf>]
- Ministry of Economic Affairs, 2004. *TechnoPartner action programme: from knowledge to prosperity*. Ministry of Economic Affairs, The Hague. [<http://trendchart.cordis.europa.eu/reports/documents/TP%20Action%20Programme.pdf>]

## APPENDIX 1

Dedicated life-sciences companies founded in The Netherlands in the period 2000-2004

<b>Founding year</b>	<b>Companies</b>
2000	2QR Research BV, AM-Pharma Holding BV, Avantium Technologies, CatchMabs, ChromaGenics BV, CoVaccine BV, Crystallics BV, Cyto Barr BV, Diocom, Glaucus Proteomics BV, Gull Nutraceutical BV, JARI Pharmaceuticals BV, Mercatorial BV, NutriScience BV, PamGene BV, Pantarhei Bioscience BV, Paradocs Group BV, PhytoGeniX BV, Plant Dynamics, Protein Labelling, QM Biosciences, Semaia Pharmaceuticals, ViroClinics, XenoBiosis BV, SemLab/Zoorobotics
2001	AquaCultura, BioDetection Systems BV, Cedi Diagnostics BV, Delta Pharma BV, Derphatox, Dynamics, EcoDeco BV, GendoMed, Groenendijk Genomics, Hep-Art Medical devices BV, Immunotoko BV, Key Drug Prototyping BV, MacroZyme BV, Merska BV, PharmaAware BV, PickCell Laboratories BV, ProSensa, PROXY Laboratories, Schelpdier Ponton Kweek BV, Skintec BV, Solea BV, Vaxinostics
2002	Alpha biogene, Bfactory, Bionchip BV, Chienna BV, Chiralix BV, Clea Technologies BV, C-Très BV, Enzyscreen, NovoVacs BV, Orgaplus BV, Pathofinder, PharmaTarget BV, River Diagnostics Inc., ServiceXS, Syntarga, Trytris, Check-Points BV, Viruvation, Vironovative,
2003	Agendia, Arrante Biosciences BV, Bioceros, BiOrion Technologies, BioWings, CIDRUX, Coronovative, CryptoGen, Delta Crystallon, Enzis, FluXXion, Foldyne, Immunaaffect, Lactrys, Merus BioPharmaceuticals, Mosaic Systems, Orteq, ProFibrix, Pyxis Discovery, SmartVax, To-BBB
2004	Add2X, CellCotec, Diassay, Dnage, Dolphys Medical, Drug Discovery Factory, Elana, Enceladus, FlexGen, InnoCore, LiverDoc, MicroVision Medical, ModiQuest, Mycobics, Passay, PodiCeps, ProteoNic, Recharge, SensoCom, Sensor Sense, Thrombinoscope, ZoBio.